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Pneumococcal Lipoid Nephrosis and the Relation Between Nephrosis and Nephritis. I. Clinical and Anatomical Studies. S. S. BLACKMAN, JR. 1

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PNEUMOCOCCAL LIPOID NEPHROSIS AND THE RELATION BETWEEN NEPHROSIS AND NEPHRITIS

I. Clinical and Anatomical Studies

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Received for publication January 25, 1934

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It is the object of this paper to make a careful inquiry concerning the etiology, pathogenesis, and nature of lipoid nephrosis. Data have been collected from the literature, from clinical and anatomical studies of ten examples of nephrosis in children, and as the result of experimental observations on the effect of pneumococcal toxin on the tissues of about five hundred laboratory animals. The experimental data will be described in a subsequent paper.

The rôle of bacterial infection in the etiology of nephrosis has been suggested by Marriott (1), Aldrich (2), and others. Govaerts (3) and Volhard (4) offered the explanation that chronic pneumococcal infection may be the cause of the disease. This idea, however, has received little support in the past. The theory that nephrosis is essentially different in nature from nephritis has won widespread popularity, although the *character* of the functional alterations of the kidneys is identical in both diseases. Nephrosis has been called "diabetes albuminuricus," a metabolic disease in which the kidneys are not sup-

posed to be primarily damaged, despite the fact that the albuminuria of nephritis might be considered the result of "diabetes albuminuricus" with equal justification. It has been denied that abnormal haematuria ever occurs in "pure" lipoid nephrosis, although microscopical haematuria has been described in many case reports in the literature, including those of Munk, the first ever published. The oedema of nephrosis is said to be caused purely by mechanical factors, though the presence of albumin in the urine and in the oedema fluid points clearly to some injury to both the glomerular and also the body capillaries in general. It is also claimed that the character of the histological lesions in the kidney shows nephrosis to be different in its nature from nephritis. The lesions in the kidney of the one are said to be "degenerative tubular" lesions. The histological changes characteristic of nephritis are described as inflammatory glomerular lesions. Actually, however, the so-called "degenerative tubular" changes described in nephrosis are commonly found in the kidneys of glomerulonephritis also. The lesions in glomerular capillaries responsible for the excretion of albumin and red blood cells in the urine are scarcely demonstrable in either nephrosis or nephritis. Although albumin and globulin escape through the glomerular capillaries in both diseases, the chief histological difference between them results from the formation of clots of fibrin, formed from fibrinogen, in the glomerular capsule and between capillary tufts in nephritis. It is the organization of these clots, containing sometimes red blood cells, necrotic epithelial cells, and even leucocytes, which leads to the destruction of glomeruli, eventually converted into masses of scar tissue, in the case of nephritis, and to the development of renal insufficiency.

Some of the conclusions reached during these studies differ from certain generally accepted views regarding several manifestations of lipoid nephrosis. In order therefore that there may be no doubt that the cases included here are examples of "pure" nephrosis, in order to illustrate the relation of pneumococcal infection to the disease, and to emphasize other manifestations of lipoid nephrosis in the human being, the clinical histories and anatomical findings are described in detail in each instance. The experiments to be described in a subsequent paper offer further evidence in support of the idea that nephrosis is a particular form of nephritis caused in some instances by pneumococcal toxin.

1. TEN EXAMPLES OF LIPOID NEPHROSIS IN CHILDREN

Case 1. O. J., colored boy, 2 years and 8 months old. Admitted to the hospital on October 4th, 1931. Died on October 6th, 1931. Duration of the disease, three weeks.

History: The present illness began three weeks before admission to the hospital, with a cold, fever (102°F.), and swelling of the face. The swelling disappeared in a few days. The cold persisted. A week later the swelling of the face returned. Three days before entry to the hospital generalized oedema appeared.

Course of the Disease: On admission the temperature was 103°F. The blood-pressure, systolic 94 and diastolic 50 mm. of mercury. The pharynx looked inflamed. The uvula was red and swollen. Pneumococcus Type III was cultured from the throat. The ear-drums were red. There was extreme generalized oedema, and signs of peritonitis were present. The child became drowsy and died on the third day in the hospital. *Temperature:* 103° to 104.5°F. *Urine:* Scanty. Albumin, 36 grams per liter (Esbach). The sediment contained many casts and a few leukocytes. No red blood cells were seen. The phthalein excretion was not tested. *Blood:* Haemoglobin, 60%. Red blood cells, 3,560,000, and leukocytes, 23,800 per c.mm. Wassermann, negative. Non-protein nitrogen, 55 mgm. %. Plasma proteins, 3.61 grams %. A/G ratio, 41/59. Cholesterol, 521 mgm. %.

Autopsy No. 12205: Anatomical Diagnosis: Lipoid nephrosis; anasarca; subacute ulcerative tonsillitis; lobular pneumonia, septicaemia, and fibrinopurulent peritonitis (Pneumococcus Type II).

Summary of Gross Anatomical Lesions. External Appearance: Very marked generalized oedema. *Abdominal Cavity:* Purulent exudate in the pelvis and in recesses about the intestines. Patches of fibrinous exudate on the peritoneal surfaces. *Heart:* Normal in size. Weight, 65 grams. *Lungs:* Scattered patches of lobular pneumonia in the lower lobe of the left lung, with several small abscesses. *Liver:* Periportal tissue yellow. *Intestines:* Walls oedematous. *Kidneys:* Large and swollen. Weight, 180 grams each. Surfaces smooth, and uniformly yellowish-gray in color. One or two minute haemorrhages were seen on the surface of each. Cortex wide, and yellowish-gray, in contrast to the red color of the pyramids. *Cranial Sinuses and Ears:* Not examined.

Summary of Microscopical Lesions. Pharynx and Tonsils: The epithelium of the pharynx is intact. The mucosa and submucosa are hyperaemic. The submucosa is infiltrated with polymorphonuclear leukocytes and mononuclear cells, among which there are Gram-positive diplococci. The crypts of the tonsils are filled with necrotic tissue and acute inflammatory exudate. The epithelium is densely infiltrated with leukocytes, and in places ulcerated, where polymorphonuclear leukocytes invade the lymphoid tissue below. There are many Gram-positive diplococci and other cocci in the crypts and inflamed tissue of the tonsil. *Lungs:* The left lower lobe contains confluent, haemorrhagic patches of lobular pneumonia and several small fresh abscesses. Gram-positive diplococci are found in the exudate. *Intestines:* There is a fresh exudate on the peritoneal surface.

The serosa is infiltrated with leukocytes. The submucosa is oedematous. *Pancreas:* All of the connective-tissue septa are densely infiltrated with leukocytes. There is purulent exudate in the lumen of a few ducts. *Abdominal Connective Tissue:* In the mesentery and about the adrenals there is a perivascular and somewhat diffuse accumulation of lymphocytes and plasma cells. *Liver:* Most of the liver cells contain a few finely divided fat droplets, somewhat more abundant in the cells about the portal spaces. Moderate numbers of Kupffer cells are filled with larger drops of neutral fat (Scharlach R). No iron can be stained in the liver (Prussian blue reaction). *Spleen:* Clumps of mononuclear cells are found in the pulp characteristic of the acute splenic tumor. Some of the germinal centres contain occasional cells filled with globules of fat. No haemosiderin can be stained. *Kidneys:* (1) *Glomeruli:* All of the glomeruli look essentially normal in structure. The capsular spaces are dilated like the tubules. In the cells of both the parietal and visceral epithelium there are a few small droplets of neutral fat. Occasional necrotic epithelial cells, and some converted into "colloid" droplets of cytoplasm can be found in the parietal layer. No definite lesions can be seen in the glomerular capillaries. They contain no excess number of leukocytes. The endothelial nuclei do not seem swollen. Many tufts of capillaries seem empty, and the nuclei in these areas are concentrated together. There is no definite thickening of the capillary basement membranes. (2) *Tubules:* All of the tubules in the cortex are considerably dilated and lined with flattened epithelium. The convoluted tubules are somewhat wider than the others. The lumina of most tubules contain granular débris. There are very few hyaline casts. In three microscopical sections haemorrhages are found in two tubules. The epithelial cells, besides being flattened, show the following changes. In a moderate number of tubules there are a few necrotic cells, sometimes *in situ*, sometimes within the lumen of a tubule. A few of the necrotic cells are calcified, and the tubules which contain the calcified material are usually lined with a very thin layer of deeply stained epithelial cells, apparently regenerated epithelium. The epithelium of a few tubules consists of "colloid" droplets of cytoplasm. No haemosiderin can be stained. In frozen sections stained with Scharlach R, most of the tubules in each cortical labyrinth[1] are lined with cells which contain moderate quantities of fat. In the cortical rays there is comparatively little fat in any of the tubules. There is a little fat in the epithelium of some of the tubules in the medulla. Most of the fat in the kidneys is neutral, isotropic fat. In frozen sections and fresh scrapings there are very small numbers of doubly refractile fluid crystals with Maltese crosses. (3)*Interstitial Tissue:* Between the tubules there is a considerable amount of fluid (oedema), and a few small collections of cells containing fat can be found. The blood vessels look normal.

[1] Each cortical labyrinth contains glomeruli, proximal and distal convoluted tubules, and the arched portions of the collecting tubules. The cortical rays contain the spiral portion of the convoluted tubules, part of the ascending limb of Henle's loop, and the straight collecting tubules.

Case 2. T. W., white boy, 6 yrs. old. Admitted to the hospital on November 7th, 1926. Died November 30th, 1926. Duration of the disease, one month.

History: Nine days before admission to the hospital the face began to swell. This was preceded by acute coryza, still present on admission. The legs and abdomen became swollen, and there was abdominal pain.

Course of the Disease: On admission there were signs of acute coryza, and the tonsils were injected. Massive oedema and ascites were present. Five days before death a tender, red, fluctuating mass developed below the right ear. Later, the skin of both sides of the body became red and tender, from the axillae to the brim of the pelvis. The temperature rose to 102°F., and the leukocytes were 25,000 per c.mm. There was anuria and coma for 12 hours before death. *Temperature* (mouth) varied from 96.5 to 100°F. for twenty days, with an occasional elevation to 101°F. During the last three days in the ward there was continuous fever, 100 to 102.5°F. *Urine:* Oliguria. Albumin, 5 to 10 grams per liter. The sediment contained hyaline, waxy, and granular casts, and occasional leukocytes. A few red blood cells were found on one examination. Phthalein excretion in 2 hours (two tests), 63 and 70%. *Blood:* Hgb. 92%. W. B. C. 9,800, on admission, to 25,000 per c.mm. Wassermann negative. Non-protein nitrogen, on the day after admission, 38 mgm. %. No other chemical studies of the blood were made. Blood-pressure: 118/70 mm. of mercury on admission.

Autopsy No. 9582. Anatomical Diagnosis: Lipoid nephrosis; anasarca; subacute ulcerative tonsillitis; septicaemia, fibrinopurulent peritonitis and cellulitis of skin and subcutaneous tissues of chest wall (Pneumococcus Type II).

Summary of Gross Anatomical Lesions: External appearance: Marked generalized oedema. *Pleural Cavities:* Hydrothorax (200 cc., right and left). *Abdominal Cavity:* Fibrinopurulent peritonitis (50–75 cc. of cloudy fluid with shreds of fibrin). *Heart:* Weight, 100 grams. *Liver:* Numerous scattered pale areas suggesting fat. *Kidneys:* Weight, 100 grams each. Large and swollen, with pale, smooth, yellow surfaces. Cortex 1 cm. thick. Purple gray pyramids. *Cranial Sinuses and Ears:* Not examined.

Summary of Microscopical Lesions: Tonsils and Pharynx: Some of the crypts of the tonsils contain purulent exudate, large colonies of Gram-positive cocci, and scattered Gram-positive diplococci. In places the epithelium is diffusely infiltrated with lymphocytes. The mucosa is ulcerated in an occasional crypt, and there is a fresh superficial fibrinous exudate with a few leukocytes. In the submucosa of the soft palate there is a diffuse chronic inflammation, with plasma cells and other mononuclear cells in moderate numbers. *Skin and Subcutaneous Tissues of Chest:* The epidermis is intact. There are clumps of lymphocytes about some of the sweat glands and blood vessels. In the subcutaneous fat and connective tissue there is a diffuse acute inflammation, with moderate numbers of Gram-positive diplococci. *Liver:* The central liver cells are somewhat atrophied. The other liver cells contain occasional fat droplets. A few Kupffer cells are distended with neutral fat. Most of the Kupffer cells are filled with haemosiderin. *Spleen:*

There are moderate numbers of acute splenic tumor cells. In the pulp numbers of phagocytes contain ingested red blood cells, and there are many phagocytes filled with haemosiderin. Fat stains show numerous cells in the pulp filled with droplets of neutral fat, and there are a few similar cells in the germinal centres. An occasional arteriole is swollen and hyaline in a localized segment. These areas are diffusely infiltrated with fat (Scharlach R). *Pancreas:* Many of the acinar epithelial cells contain numerous small particles of fat. *Kidneys:* (1) *Glomeruli:* None of the glomeruli is obliterated or even partly hyalinized. There is no inflammation of the glomeruli, *i.e.*, no accumulation of leukocytes, and there are no crescents in the capsular spaces. The latter are not apparently dilated. The glomerular epithelium, in both the parietal and visceral layers, can be plainly seen. A few of these cells contain droplets of fat, and the cytoplasm of a few is in the form of "colloid" droplets. A few necrotic glomerular epithelial cells are found. In a moderate number of diffusely scattered glomeruli there are small tufts of capillaries covered by a syncytial mass consisting of three or four large epithelial cells. Occasionally these form adhesions with the parietal layer of the capsule. None of these is associated with hyalinized or obliterated capillaries. Some of the glomerular capillaries are empty, and such empty tufts show numbers of nuclei concentrated together. The nuclei are not apparently more numerous than normal. The walls of these capillaries look thicker than the walls of capillaries which are filled with blood, but it is impossible to say that they actually are thickened, since the empty capillaries are somewhat collapsed. One or two capillaries in a moderate number of glomeruli contain fresh fibrin thrombi. (2) *Tubules:* In each cortical labyrinth most of the tubules are moderately dilated. They are lined with rather plump cuboidal cells which take a deep purplish stain with haematoxylin and eosin, resembling regenerated cells, and occasionally showing mitotic figures. A good many of these tubules contain hyaline and granular casts, and in a few there are small numbers of polymorphonuclear leukocytes. Moderate numbers of these tubules show fresh necrosis of a few cells here and there. Some are within the lumen of tubules. Others remain *in situ*. A few cells contain droplets of colloid-like cytoplasm. Some of the necrotic cells are calcified. A few small groups of widely scattered tubules in the cortex contain fresh red blood cells. The spiral parts of the convoluted tubules, which lie in the cortical rays, in contrast to those just described, are lined with very large, almost columnar epithelial cells having an extremely coarse, bright pink, granular cytoplasm. There are very few casts in these tubules. Their lumina are in places dilated, but are often nearly filled by the large swollen cells. Very few of these cells are necrotic, although an occasional one can be found. The collecting tubules seem little affected. Fat stains (Scharlach R) of frozen sections show large quantities of fat in the epithelial cells of most tubules in each cortical labyrinth. In the cortical rays there is very little fat in the epithelium of any of the tubules. Even those lined with very large cells having a coarse cytoplasm are almost devoid of fat. The last portions of the convoluted tubules which extend from the cortical rays into

the medulla do contain large numbers of fat droplets within their epithelial cells. Under the polarizing microscope frozen sections show numerous doubly refractile fluid crystals with Maltese crosses, cholesterol esters, which disappear on being heated and reappear on cooling. A few of these are found in glomeruli. Most of them are in the fat-laden epithelium of tubules in each cortical labyrinth, and in the interstitial tissue. (3) *Interstitial Tissues:* Between the tubules in each cortical labyrinth there are numerous coarse particles of fat, sometimes held within large phagocytes. There is very slight oedema. The blood vessels look normal.

Case 3. G. A., colored girl, 17 months old. Admitted to the hospital on August 24th, 1931. Died on September 16th, 1931. Duration of the disease, six weeks.

History: Three weeks before admission to the hospital there was fever for several days which subsided and was followed by oedema of the lower extremities and swelling of the abdomen.

Course of the Disease: At the time of admission to the hospital there was generalized oedema with ascites. Signs of acute pharyngitis and otitis media were present, with slight fever, 100.4°F., and leukocytosis, 15,500 per c.mm. The right ear-drum was punctured and drained (no cultures reported). About two weeks after admission, signs of peritonitis developed and persisted for ten days until death. *Temperature:* Except for slight fever on the day of admission, the temperature was subnormal until the onset of peritonitis. *Urine:* Oliguria. Albumin, 8 to 10 grams per liter. The sediment contained few granular and hyaline casts. No red blood cells were seen. Phthalein excretion not tested. *Blood:* Haemoglobin, 85%. Red blood cells, 4,690,000 per c.mm. Leukocytes, 15,000 to 36,000 per c.mm. Non-protein nitrogen 28 to 32 mgm. %. Plasma proteins, 3.82 to 3.84 gm. %. A/G ratio 38/62 to 40/60. Cholesterol, 600 mgm. %. *Blood Pressure:* Systolic 90 and diastolic 60 mm. of mercury.

Autopsy No. 12176. Anatomical Diagnosis: Lipoid nephrosis; generalized oedema; septicaemia and fibrinopurulent peritonitis (Pneumococcus Type II).

Summary of Gross Anatomical Lesions: External Appearance: Marked generalized oedema. *Abdominal Cavity:* A thin greenish-yellow exudate with shreds of fibrin was found in the pelvis and lumbar hollows. There were patches of fibrinous exudate on the peritoneal surfaces. *Heart:* Not enlarged. Weight, 60 grams. *Liver:* Showed patches of yellow mottling. *Kidneys:* Swollen, pale, and grayish-yellow in color. Surfaces smooth. Cortex wide. Pyramids red. Weight, 70 and 80 grams, respectively. *Tonsils, Ears and Cranial Sinuses:* Not examined.

Summary of Microscopical Lesions: Abdominal Connective Tissue: Besides evidence of acute peritonitis, there is a chronic inflammatory reaction in the serosa of the intestine, about the adrenal, and in the peritoneal covering of the Fallopian tubes. In these tissues there are small numbers of diffusely scattered lymphocytes and plasma cells, and also perivascular collections of the same leukocytes. *Pancreas:* In connection with the fresh peritonitis there are numerous patches of necrotic connective tissue in the septa of the pancreas. There are also a number

of focal fat necroses and areas of necrosis of the pancreatic tissue. These are all usually associated with fibrinous exudate and contain very numerous pneumococci, but there are hardly any leukocytes concerned in the inflammatory reaction. *Colon:* The microscopical sections show several areas of superficial necrosis of the mucosa, covered with fibrinous exudate containing myriads of organisms, many of which are Gram-positive diplococci. *Liver:* Many of the Kupffer cells contain small globules of neutral fat (Scharlach R). The liver cells are practically free from stainable fat. There is also some iron pigment in most of the Kupffer cells. The liver cells contain none. *Spleen:* In the pulp there are numerous phagocytes with ingested red blood corpuscles and haemosiderin. In most of the Malpighian bodies a few cells are found filled with globules of neutral fat. *Kidneys:* (1) *Glomeruli:* There are neither hyalinized, obliterated glomeruli, nor crescents in four sections examined. The glomerular capillaries show no apparent increase in the number of endothelial nuclei or leukocytes. In many glomeruli some of the capillaries are distended with fresh thrombi. The capsular spaces are moderately dilated and contain granular débris. The glomeruli show conspicuous bare-looking capillary walls with epithelial and endothelial nuclei. There are a very few widely scattered capillary tufts partly covered by large, deeply stained, regenerated epithelial cells which rarely are continuous with similar small groups of cells in the parietal layer of the capsule, thus forming small adhesions. Occasionally the cytoplasm of these cells is in the form of "colloid" drops, and rarely such cells are necrotic, with fragmented nuclei. In frozen sections many glomeruli contain a few cells with small droplets of fat (Scharlach R). Some of the fat-holding cells can be identified as epithelium. Others, which lie among the capillary loops, cannot be identified. The walls of the glomerular capillaries are not definitely thickened (McGregor's connective-tissue stain). Where the capillaries contain blood or thrombi, their walls are thin and delicate. The walls of empty capillaries look somewhat thicker. (2) *Tubules:* In the cortex practically all of the tubules are wide, and seem almost uniformly and equally dilated. Most of them contain granular débris, and in a few there are hyaline casts. The convoluted tubules are slightly wider than the collecting tubules in the cortex, but the latter are distinctly altered. In five sections there are three or four groups of tubules containing fresh haemorrhages. Most of the tubules are lined with low cuboidal or even flatter epithelium. Many tubules in the superficial part of the cortex and in each labyrinth are lined with very thin, deeply stained, regenerated cells. One can find a few necrotic cells, and occasional clumps of calcified necrotic cells. A few cells have been converted into colloid-like drops of cytoplasm. There is no pigmentation of the epithelium with haemosiderin. Frozen sections show very moderate numbers of fat droplets in many of the cells lining some of the tubules in each cortical labyrinth. A few tubules in the cortical rays contain very small numbers of fat droplets, and in the pyramids a few contain a little fat within their epithelium. Under the polarizing microscope numerous typical doubly refractile fluid crystals, cholesterol esters, can be demonstrated. Most of the fat, however, is neutral,

isotropic fat. (3) *Interstitial Tissues:* Between the tubules there is some oedema, and in each cortical labyrinth a few wandering cells contain neutral and doubly refractile fat. The blood vessels look normal.

Case 4. R. G., white boy, 8 years old. Admitted to the hospital on August 5th, 1932. Died on September 15th, 1932. Duration of the disease, 7 weeks.

History: In this case oedema was the first sign of the disease to be observed. It appeared about twelve days before the child was admitted to the hospital. On the day of admission there was a moderate degree of generalized oedema with ascites, slight fever, 100.7°F., and leukocytosis, 10,340 per c.mm. The fever and leukocytosis were unexplained. For nearly a month before death there were frequent complaints of abdominal pain with vomiting. A week before death the child complained of a sore throat, and for 48 hours there were signs of peritonitis, with high fever, 104–105°F., and leukocytosis, 16,000 per c.mm. Erysipelas-like lesions developed in the skin of the thighs. *Temperature:* (Rectal) Usually normal. Occasionally elevated to 100.4°F. before peritonitis developed. *Urine:* Scanty. Volume varied from about 200 to 500 cc. daily. Albumin, 4 to 14 grams per liter. The sediment contained hyaline and granular casts, and white blood cells. Very few red blood cells were seen on three examinations, before the onset of definite signs of peritonitis. *Blood:* Haemoglobin 105%. Red blood cells, 5,250,000 per c.mm. Leukocytes: varied from 9,900 to 11,120 per c.mm. before the onset of peritonitis. Non-protein nitrogen, 34.3 to 38.5 mgm. %; plasma proteins, 2.87 to 4.1 gm. %; A/G ratio, 0.67 to 0.77. Cholesterol, 394 to 526 mgm. %. Wassermann, negative. *Blood-pressure:* 110/80 on admission. *Bacterial Cultures:* Alpha and Beta Streptococci, and Pneumococci Type IV were cultured from the pharynx when the boy complained of sore throat.

Autopsy No. 12775: Anatomical Diagnosis: Lipoid nephrosis; anasarca; septicaemia, serofibrinopurulent pleurisy, pericarditis, and peritonitis (Pneumococcus Type IV).

Summary of Gross Anatomical Lesions: External Appearance: Marked generalized oedema. *Body Cavities:* There was turbid fluid in the abdominal cavity (300 cc.) and thick green purulent exudate in the pelvis. Fluid containing shreds of fibrin was found in each pleural cavity (150–200 cc.), and there were approximately 40 cc. of similar exudate in the pericardial sac. *Heart:* Weight, 125 grams. Not enlarged. *Liver:* Scattered irregular pale yellow patches on the cut surface. *Spleen:* Moderately enlarged. Weight, 75 grams. *Kidneys:* Greatly swollen, weighing 140 and 160 grams, respectively. External surfaces smooth, uniformly yellow in color. Widely scattered punctate haemorrhages. Cortical striae straight. Cortex pale and pyramids red. *Tonsils:* Partly removed. Small masses of lymphoid tissue in right tonsillar fossa. *Cranial Sinuses and Ears:* Not examined.

Summary of Microscopical Lesions: Tonsils: The crypts of the remaining pharyngeal adenoid tissue contain many Gram-positive diplococci, and other cocci.

In places the squamous-cell epithelium is vascularized and densely infiltrated with mononuclear leukocytes which have caused widespread separation of the epithelial cells. In such places a few diplococci can be found. The surface epithelium is in places infiltrated with moderate numbers of polymorphonuclear cells *Lung:* On the pleura there are small patches of fibrinopurulent exudate. *Liver:* The central liver cells are slightly atrophied. The periphery of every lobule is outlined by a narrow zone of cells filled with fat globules. The rest of the liver cells contain a few small finely divided globules of neutral fat. Many of the Kupffer cells are filled with fat. The fat is more abundant in the liver than in the kidney. The Kupffer cells are diffusely pigmented with haemosiderin. The liver cells contain none. *Spleen:* There are collections of mononuclear cells in the pulp characteristic of the acute splenic tumor, and many large phagocytes engorged with red blood corpuscles and granules of haemosiderin are present. Numerous large cells in the pulp and in the germinal centres are filled with particles of neutral fat. The walls of many of the arterioles in the Malpighian bodies have the hyaline appearance seen in association with generalized arteriolosclerosis, and fat stains show that the walls of these vessels are uniformly infiltrated with fat, although the arterioles in the kidneys and other tissues are not affected. *Thyroid:* In one lobe there is an area of fresh necrosis, two or three millimetres in diameter, including several small lobules. Throughout the necrotic tissue there is a network of fibrin, and clouds of diplococci can be stained. There is practically no exudate of leukocytes. *Bone-marrow:* (Rib and Vertebra) Normal. *Fat Stains:* In the heart and voluntary muscle there are scattered groups of fibres containing finely divided and some larger particles of neutral fat. The acinar and islet cells of the pancreas contain numerous small fat particles, and in the lung many of the alveolar epithelial cells are filled with somewhat larger droplets of fat. *Kidney:* (1) *Glomeruli:* The capillaries of all of the glomeruli look essentially normal. No glomeruli are hyalinized. There are no crescents. One can rarely find small patches of large epithelial cells covering parts of a capillary tuft, occasionally adherent to the parietal layer of the capsule. A few epithelial cells in nearly every glomerulus contain small particles of fat, and occasionally a large cell filled with fat can be seen within a glomerular capillary. In one section of each kidney four or five patches of tubules are found with fresh haemorrhage. (2) *Tubules:* The tubules are only a little widened. In general the tubular changes are very slight. There are very few casts in the cortex. Many collecting tubules in the pyramids are filled with hyaline casts. In the superficial part of the cortex and about some of the glomeruli deeper in the cortex there are numerous small patches of tubules lined with deeply stained, regenerated epithelial cells which are somewhat flattened. Among these tubules necrotic cells and small calcified masses can be found in small numbers. There is no change in the cells lining the rest of the tubules other than well marked cloudy swelling. Rarely, cells converted into "colloid" drops of cytoplasm can be found. Relatively few of the tubules in each cortical labyrinth contain small amounts of fat within the epithelial cells, and between these tubules are small clumps of finely

divided fat. In the cortical rays the tubules are practically free from fat. There is a little fat in some of the cells of the collecting tubules and in Henle's loops in the medulla. Only a few doubly refractile fluid crystals, cholesterol esters, can be found in scrapings and frozen sections under the polarizing microscope. A few scattered groups of tubules in the cortex are diffusely pigmented with granules of haemosiderin. (3) *Interstitial Tissue:* There is no oedema. The blood vessels look normal.

Case 5. J. H., white boy, 4½ years old. Admitted to the hospital on February 25th, 1924. Died August 2nd, 1924. Duration of the disease, 5½ months.

History and Course of the Disease: The present illness began with sore throat, one week before admission to the hospital. Four days later the face and abdomen began to swell. There was anuria for 3 days.

On admission there was slight fever, 100.4°F., leukocytosis of 10,150 per c.mm., signs of chronic tonsillitis, dental caries, and anasarca. During the next five months oedema and albuminuria were variable. The oedema nearly disappeared at times. In March, with an attack of sore throat, acute rhinopharyngitis (no cultures made) and high fever, 103°F., the albumin in the urine rose to 11 grams per liter. Four days previously there had been no albumin in the urine. In April, abscesses were found about several teeth. These were treated, and the tonsils were removed. For the next three months the oedema and albuminuria increased. On July 22nd, the pharynx was diffusely reddened, the temperature rose to 104°F., and signs of peritonitis appeared, with a leukocytosis of 38,000 per c.mm. The child died eleven days later, with increasing oedema. *Temperature* (rectal): For 5 months there was some fever on at least one day nearly every week. It was often above 100°F. and reached 101°F. or above on a good many occasions. Records of subnormal temperature, 97°F., are extremely numerous on the chart. At the end, with peritonitis, there was high irregular fever. *Urine:* Scanty when there was marked albuminuria. The albumin varied from none to 11 grams per liter. The sediment contained numerous casts at times. No red blood cells were ever found. The phthalein excretion was 50% in two hours. (Intramuscular injection of phthalein four days after admission.) *Blood:* Wassermann negative. No other examinations made. *Blood-pressure:* 118/80 on admission.

Autopsy No. 8162. Anatomical Diagnosis: Lipoid nephrosis; generalized oedema; septicaemia, lobular pneumonia, and fibrinopurulent peritonitis (Pneumococcus Type IV).

Summary of Gross Anatomical Lesions: External Appearance: Marked generalized oedema. *Abdominal Cavity:* Serofibrinopurulent peritonitis (1500 cc.). There was a thick, soft, greenish exudate in the pelvic cavity and behind loops of small intestine. *Lungs:* Oedematous, with a few small patches of consolidation, and slight fibrinous pleurisy. *Heart:* Weight, 75 grams. Not enlarged. *Intestine:* Oedema of the colon. *Liver:* Periportal tissue yellow in color. *Kidneys:* Weight, 140 and 145 grams, respectively. Greatly swollen and soft. Surfaces

smooth and pale. Cortex 1 cm. thick, yellowish-gray. Striae straight but blurred. No scars or haemorrhages seen. Pyramids red. *Neck Organs:* Tonsils removed at operation. Pharyngeal mucosa injected. *Cranial Sinuses and Ears:* Not examined.

Summary of Microscopical Lesions: Tonsil: Not studied. No sections were made of the pharyngeal tissues. *Larynx and Lung:* The mucosa of the larynx is ulcerated and covered with a diphtheritic exudate for a distance of 1 cm. At the same level the opposite walls of the oesophagus show a similar diphtheritic inflammation, and chronic inflammation in the submucosa, with lymphocytes and plasma cells. There are a few minute foci of lobular pneumonia. *Abdominal Connective Tissue:* On the surface of the liver, intestines, and mesentery there are patches of fibrinopurulent exudate. In the capsule of the liver, in the serosa and muscularis of the intestine, along the connective-tissue bands in the mesentery, and between pancreatic lobules there is a marked chronic inflammatory reaction, characterized by large numbers of lymphocytes and plasma cells. *Liver:* There is a wide band of liver cells in the periphery of each lobule filled with fat globules. Very few of the other liver cells contain any fat. A few Kupffer cells are filled with small fat particles, and every Kupffer cell is pigmented with haemosiderin. *Spleen:* The germinal centres contain phagocytes filled with particles of neutral fat, and there are a few similar fat-laden cells in the splenic pulp. In the pulp, too, are very numerous phagocytes with red blood corpuscles and granules of haemosiderin. The walls of many of the arterioles in the spleen are infiltrated with fat, diffusely, or in hyaline segments. *Pancreas:* The acinar cells contain a few small drops of fat. The arterioles show none. *Kidneys:* (1) *Glomeruli:* None of the glomeruli shows any inflammation or hyalinization. There are no crescents. Most glomeruli are rather small and contain little blood in the capillaries. The capsular spaces are a little dilated. In the epithelium of both layers of the capsule of many of the glomeruli there are a few particles of neutral fat. One can find a few small adhesions between an occasional tuft of capillaries and Bowman's capsule, and tufts are rarely found covered by several large regenerated epithelial cells with purplish cytoplasm and large vesicular nuclei. The glomerular capillaries which contain blood look normal. The walls of empty capillaries look somewhat thicker. In three sections, red blood cells are found in very few groups of tubules. (2) *Tubules:* In each cortical labyrinth the tubules are moderately dilated and lined with epithelial cells having the characteristics of regenerated cells. There are also a good many rather elongated patches of tubules which are somewhat atrophied and separated from each other by a little scar tissue in the interstitial spaces, sometimes associated with a few lymphocytes. Among such patches there are occasional atrophied glomeruli. None of these is hyalinized, however. The dilated tubules are lined with cells which show cloudy swelling, and there are occasional necrotic cells, some regenerated ones, and a few small clumps of calcified material. An occasional cell shows "colloid" drops of cytoplasm. In each cortical labyrinth many of the tubules contain fat droplets which fill up the epithelial

cells, and between these tubules there are collections of fat, sometimes within large phagocytes. Part of the fat is in the form of typical doubly refractile fluid crystals which show Maltese crosses, disappearing when heated. In the cortical rays the collecting tubules are a little dilated. The spiral portions of the convoluted tubules, which lie in the cortical rays, are very much dilated. Their epithelial cells are large and pale, with extremely coarse granular cytoplasm. These cells contain practically no fat except in the lower portions of the tubules which project into the upper part of the medulla. Many of the collecting tubules in the pyramids contain small droplets of neutral fat in some of their lining cells. (3) *Interstitial Tissue:* There is no oedema. The blood vessels appear normal.

Case 6. R. C., white girl, 5 years old. Admitted to the hospital February 4th, 1929. Died, May 10th, 1929. Duration of the disease, 7¼ months.

History and Course of the Disease: About the first of October the child "caught a very bad cold," and suddenly began "to swell up." She was very oedematous for two months. Towards the end of November the oedema almost disappeared, but returned again early in December. For two months, in December and January, there was abdominal pain at times.

On the day of admission, four months from the onset of the disease, the child was oedematous and there was ascites. The pharynx and tonsils were described as "deeply injected," and the tonsils were somewhat enlarged and "ragged" in appearance. There was a leukocytosis of 13,800 per c.mm. without fever on admission. For two months the signs and symptoms of nephrosis were more or less stationary, and she was discharged on April 6th. She remained at home in bed for a month, without any improvement. On May 8th she was readmitted, with a history of abdominal pain and diarrhoea for several days. She was extremely oedematous, and delirious. There was high fever, 104–105°F. The throat was diffusely reddened, and the tonsils red and ragged as before. She died 52 hours later. *Temperature* (rectal): During the first admission, there was slight unexplained fever, 100–100.4°F., on one or more days a week for four of the nine weeks in the hospital. *Urine:* The volume varied from 400 to 1,200 cc. in 24 hours (first admission). The specific gravity was high at times (1.030). Albumin, 1 to 30 grams per liter. The sediment contained many casts of various kinds at times. There were variable numbers of leukocytes. A few red blood cells were seen on two examinations, once during the first, and once on the second admission to the hospital. Phthalein excretion, 45% in one hour (first admission). *Blood:* Haemoglobin, 105%. Red blood cells, 5,290,000 per c.mm. (first admission). Haemoglobin, 65% (second admission). Wassermann negative. Non-protein nitrogen, 46 mgm. %. Plasma proteins, 1.52 grams %. Cholesterol, 410 mgms. %. No blood chemistry studies were made on the second admission. *Blood-pressure:* Not taken.

Autopsy No. 10902. Anatomical Diagnosis: Lipoid nephrosis; anasarca; slight pneumococcal lobular pneumonia and serofibrinous peritonitis (organism not typed).

Summary of Gross Anatomical Lesions: External Appearance: Marked generalized oedema. *Abdominal Cavity:* Contained 100 cc. of blood-stained fluid with shreds of fibrin. *Pleural Cavities:* The left contained 100 cc. of blood-stained fluid with shreds of fibrin. The right contained 50 cc. of clear fluid. *Heart:* Weight, 110 grams. Not enlarged. *Lungs:* A few small areas of consolidation were found in the base of the left lung. *Intestines:* Marked oedema of the submucosa of the colon. *Kidneys:* Weight, 120 and 130 grams, respectively. Greatly swollen. Surfaces smooth and yellow. One or two minute superficial haemorrhages. Cortex, about 10 mm. thick, pale, and yellowish in color. *Spleen:* Somewhat enlarged. Weight, 90 grams. Pulp swollen, dark red. *Tonsils:* The crypts contained solid material. *Cranial Sinuses and Ears:* Not examined.

Summary of Microscopical Lesions: Tonsil: The crypts contain large colonies of Gram-positive cocci and diffusely scattered Gram-positive diplococci, together with some purulent exudate. In one crypt the epithelium is destroyed in patches. The superficial tissue is necrotic, and on the surface there is a diphtheritic exudate in which there are many Gram-positive diplococci. The blood vessels in the lymphoid tissue are hyperaemic, and throughout the lymphoid tissue there are masses of Gram-positive diplococci. At the margin of the tonsil the pharyngeal mucosa is intact. Beneath it there is a patchy chronic inflammation about blood vessels and ducts. *Lung:* In one lung there are a few minute areas of fresh pneumonia containing pneumococci (stained and cultured). *Abdominal Connective Tissues:* In the fat and connective tissue at the hilum of the spleen, about the pancreas and along its septa, in the loose tissues about the adrenal, and in the peritoneal surface of the colon, there is a diffuse acute inflammation with many Gram-positive diplococci. In all of these places there are scattered irregular foci of necrosis of the connective tissue, with accumulations of fibrinopurulent exudate. In and about the pancreas, in addition, are scattered fresh fat necroses. There is a diffuse subacute inflammation in the submucosa of the colon. *Adrenal:* Throughout the cortex there are numerous small foci of necrotic cells without any inflammatory reaction. *Pancreas:* Nearly all of the acinar and islet cells contain numerous small particles of fat. *Liver:* Most of the liver cells contain numerous small droplets of fat. The periportal cells contain more fat than the others. Some of the Kupffer cells are also filled with particles of neutral fat, and some are diffusely pigmented with haemosiderin. *Spleen:* Numerous accumulations of mononuclear cells, characteristic of the acute splenic tumor, are present. There are numerous phagocytes which contain red blood cells and granules of haemosiderin. In the pulp there are many cells laden with fat. *Heart:* Throughout the myocardium there are a few scattered small haemorrhages. *Bone-marrow:* (Rib and Vertebra): Normal. *Kidneys:* (1) *Glomeruli:* All of the glomeruli look practically normal in structure. They are not inflamed and there are neither crescents nor hyalinized glomeruli. In paraffin sections the glomeruli look small, and the capsular spaces are wide, containing desquamated epithelial cells and granular débris. Numerous glomeruli contain small clumps of neutral fat some of which can be

identified within epithelial cells. With careful search an occasional small adhesion can be found between a few large epithelial cells covering the surface of a tuft and a small patch of similar cells lining the parietal layer of the capsule. Most of the glomerular capillaries seem empty. This exaggerates the appearance of the capillary walls, but it is impossible to be certain that there is any actual thickening of the tissue. The walls of the capillaries filled with blood are thin and delicate. In four sections only five or six groups of tubules are found with red blood cells in the lumina. (2) *Tubules:* In the cortex all of the tubules are wide, with flattened epithelial lining. The convoluted tubules are nearly uniformly and equally widened, and are somewhat more dilated than the other tubules. Where the convoluted tubules lie deep in the cortex and in the upper part of the medulla they are more dilated than above in the cortex. Nearly all of the tubules in the cortex contain a pink, granular, material. In a few there are solid casts. Most of the tubular epithelium shows cloudy, granular cytoplasm. Colloid droplets of cytoplasm can be found rarely in a few cells. There are practically no necrotic cells, and no calcified masses. The epithelium is not pigmented with haemosiderin. Fat stains of frozen sections show the epithelium of moderate numbers of tubules in each cortical labyrinth filled with fat particles, and there are numerous large collections of fat between these tubules. Under the polarizing microscope, in frozen sections and in smears of scrapings, there are numerous doubly refractile fluid crystals exhibiting the Maltese crosses. The tubules in the cortical rays contain practically no fat. The epithelium of Henle's loops and of many of the collecting tubules in the pyramids contain large quantities of neutral fat, and fat is more abundant in the tubules of the medulla than in the convoluted tubules in the cortex. (3) *Interstitial Tissue:* The tissue between the tubules in the cortex is quite oedematous. The blood vessels look normal.

Case 7. T. S., colored boy, 5 years old. Admitted to the hospital first on November 29th, 1930. Died on August 20th, 1931. Duration of the disease, 9 months.

History: For five months in 1927, from April to September, the child was frequently seen in the dispensary with colds, nasal discharge, otitis media, and fever (100–102°F.). One year and a half later, in April and May, 1929, he was again treated in the dispensary for bilateral otitis media. The left ear drum was perforated. The tonsils were large and looked inflamed. There was slight fever, 100°F. In November 1930, at the age of four years, generalized oedema appeared, and he was brought into the hospital at the end of November with signs of chronic tonsillitis, nephrosis, and secondary anaemia. He was in the hospital for seven weeks. Towards the end of January most of the oedema had disappeared, and he was discharged on January 18th, 1931. *Temperature:* (rectal): There was some fever, 100–100.4°F., during six of the seven weeks on two or more days each week. The temperature rose occasionally to 101°F. *Urine:* The volume varied. At times there was oliguria. The albumin varied from 20 grams per liter on ad-

mission to $\frac{1}{8}$ gram per liter on discharge. The sediment contained many casts at times, and some leukocytes. Often no red blood cells were found, but on numerous occasions 10–15 red cells per high-power microscopic field were seen. Phthalein excretion: 75% in 2 hours. *Blood:* Wassermann negative. Haemoglobin, 76%; red blood cells, 3,920,000 per c.mm. White blood cells 9,700 per c.mm. on admission. Haemoglobin $1\frac{1}{2}$ months later, 65%. *Blood Chemistry:* Non-protein nitrogen on admission was 71.7 mgm. %. Two days later it was 46.6 mgm. %. Plasma proteins were 4.07 gm. %. A/G ratio inverted (0.62). Cholesterol, 500 mgm. %. Before discharge from the hospital the non-protein nitrogen was 36.4 mgm. %. The total plasma protein was 5.33 gm. %. A/G ratio inverted (0.98), and the cholesterol 500 mgm. %. *Blood-pressure:* Varied from 120/90 to 90/65.

Course of Disease: Two days after discharge oedema reappeared, and he was brought back into the hospital for a month. For two weeks there was irregular fever, 101–102°F. often, with stomatitis and pharyngitis. On admission the leukocytes were 15,950 per c.mm. The oedema and albuminuria diminished during this time, and disappeared. The urine at first contained many leukocytes and casts, and 4 grams of albumin per liter. A few red blood cells were found on one examination. *Blood-pressure:* From 120/78 to 100/75. On one occasion the pressure was found to be 130/100 mm. of mercury. *Blood-chemistry:* Non-protein nitrogen, 46 to 22 mgm. %. Total proteins, 4.14 to 5.75 gram %. A/G ratio, 0.68 to 1.06.

He was discharged once more and for four months seemed well. In June he had a "head cold" for about ten days. Following this, on June 15th, 1931, oliguria and oedema returned. On the third hospital admission there was anasarca, with a red throat and nasal discharge. The urine contained 5 grams of albumin per liter, white blood cells, and many casts. Occasional red blood cells were found on a good many examinations. The phthalein excretion was 55% in 2 hours. For a month the condition was more or less stationary. The tonsils were removed. Following this for a few days the amount of albumin in the urine increased, from 1 to 7 grams in 24 hours. Then the albuminuria and oedema gradually decreased, and he was discharged again, August 6th, 1931, with slight albuminuria. On a good many days during this admission, before and after the tonsils were removed, there was some fever, 100.4°F., and once on the day of discharge it reached 102°F. *Blood:* Haemoglobin, 85%. Red blood cells, 4,400,000 per c.mm. White blood cells, 12,000 per c.mm. on admission. *Blood Chemistry* (third admission): Non-protein nitrogen, 30.5 mgm. %. Total proteins, 3.78 mgm. %. A/G ratio, inverted (0.65). Cholesterol, 750 mgm. %. Chemistry at time of discharge; Non-protein nitrogen, 25.2 mgm. %. Total proteins, 5.16 gm. %. A/G ratio 1.11. Cholesterol 857 mgm. %. *Blood-pressure:* 118/80 to 80/60 mm. of mercury.

Six days after leaving the hospital the oedema reappeared, and he was admitted to the ward once more, with anasarca, and lived only nine days. The temperature, usually subnormal, rose to 100.6°F. on the fourth day, and on the

seventh day suddenly went up to 103°F. There were signs of peritonitis for two days. *Urine:* Scanty. Albumin, 16 grams per liter. The sediment contained casts, and leukocytes, and 4–5 red blood cells per high-power microscopic field were found on two examinations. *Blood:* Non-protein nitrogen, 35 mgm. %. Total proteins, 3.14 grams %. A/G ratio, 24/76. Cholesterol, 769 mgm. %.

Autopsy No. 12135. Anatomical Diagnosis: Lipoid nephrosis; septicaemia, pericarditis, pleurisy and peritonitis (Pneumococcus Type IV).

Summary of Gross Anatomical Lesions: External Appearance: Moderate generalized oedema. *Pleural Cavities:* Each contained 40 to 70 cc. of thin, clear, fluid with clots of fibrin. *Pericardial Cavity:* Contained a small amount of thin fibrinopurulent fluid. *Abdominal Cavity:* Distended with cloudy fluid containing opaque clots. Peritoneal surfaces dull in appearance, covered here and there with fibrinous exudate. *Heart:* Not enlarged. Weight, 110 grams. *Lungs:* Pleural surfaces dull, finely granular, covered in places by thin layers of fibrin. *Spleen:* Moderately enlarged. Weight, 55 grams. *Intestines:* Walls oedematous. *Kidneys:* Large and yellow. Weight, 120 grams each. Surfaces flecked with scattered minute haemorrhages. Cortex thick, greatly swollen and yellow. Pyramids dark. *Liver:* Scattered yellow areas suggesting fat. *Tonsils:* Removed at operation.

Summary of Microscopical Lesions: Pharynx: No microscopical sections were made at autopsy. *Abdominal Connective Tissues:* Along the septa of the pancreas and in the serous layer of the colon there are conspicuous perivascular collections of lymphocytes and plasma cells. *Liver:* Most of the liver cells and many Kupffer cells contain numerous fat droplets. There is more fat in the periportal liver cells than in the others. Many of the Kupffer cells are pigmented with haemosiderin. *Spleen:* The pulp contains clumps of mononuclear cells characteristic of the acute splenic tumor. There are also many mononuclear phagocytes containing haemosiderin and ingested red blood cells. In the germinal centres and in the pulp there are phagocytes in small numbers filled with globules of neutral fat. The walls of some of the arterioles look hyaline, and are diffusely infiltrated with fat. *Pancreas:* Most of the acinar epithelium contains many small fat globules, and occasional arterioles are hyaline, their walls infiltrated with fat. *Kidneys:* There are a few scattered focal scars, usually in the superficial layer of the cortex. One can be found in nearly every low-power microscopical field. They are narrow, elongated scars, more or less parallel to each other and to the tubules. Each one contains one or two partly or completely obliterated, hyalinized glomeruli, surrounded by a group of atrophied and calcified tubules. Between the latter there is a little scar tissue infiltrated with a few lymphocytes. In some of the scarred areas small masses of calcified material can be found, usually within tubules. *Glomeruli:* The glomeruli throughout the rest of the cortex look essentially normal in structure. They are not inflamed and there are no crescents. Some of the epithelial cells in most glomeruli contain small clumps of finely divided fat droplets, and in some glomeruli there are doubly refractile fluid lipoid crystals exhibiting Maltese

crosses. There are rare small adhesions between capillary tufts and Bowman's capsule, and occasionally large regenerated epithelial cells can be found covering loops of a few capillary tufts. In most of the glomeruli some of the capillaries contain little or no blood. The walls of these capillaries look thicker than the walls of capillaries filled with blood. The nuclei of epithelial and endothelial cells associated with the empty capillaries are concentrated together, but are not apparently more numerous or larger than normal. No thrombi are found in any of the glomerular capillaries. One small fresh haemorrhage can be found in a tubule in nearly every low-power microscopical field. *Tubules:* The convoluted tubules are moderately and nearly uniformly widened. The spiral segments of the proximal convoluted tubules in the cortical rays, and their straight extensions in the upper layer of the medulla, are somewhat wider than other segments of these tubules. Most of the tubules contain granular débris. There are very few solid casts either in the cortex or pyramids. The epithelial cells of the widest tubules are rather large, with very coarse granular cytoplasm. Some are vacuolated. The cells lining the other segments of the convoluted tubules are somewhat flattened. Their cytoplasm has the appearance of cloudy swelling. About some of the glomeruli there are small groups of tubules lined with flat, regenerated cells. In some of these there are small calcified masses. Very few necrotic cells can be found in an occasional tubule, and the cytoplasm of a few cells is in the form of colloid-like droplets. A few groups of tubules in the cortex are pigmented with haemosiderin. The amount of fat in these kidneys is very moderate (Scharlach R). As in the other cases, it has a distinct radial arrangement in the cortex. Most of it is within the epithelium of some of the tubules of each cortical labyrinth, and in small clumps between these tubules. As in the other cases, there are some convoluted tubules with little or no fat. The dilated spiral portions of the proximal convoluted tubules are practically without fat where they lie in the cortical rays, but the cells lining the last straight segments of the proximal convoluted tubules which dip into the upper part of the medulla are more or less filled with fat droplets. In the medulla the epithelium of some of the loops of Henle is filled with fat, and a few of the collecting tubules in the cortex and medulla show small numbers of neutral fat droplets. Much of the fat in the cortex is neutral fat, but there are also numerous small doubly refractile fluid lipoid crystals showing Maltese crosses which appear in frozen section, cooled after being heated. *Interstitial Tissue:* There is no oedema of the interstitial tissue. The blood vessels look normal. Their walls contain no stainable fat (Scharlach R).

Case 8. M. C., white girl, 3 years old. Admitted to the hospital on February 22nd, 1922. Died, February 18th, 1923. Duration of the disease, one year.

History: The first symptoms were loss of appetite and vomiting for several days during the first week of January, 1922. On the fourth day, oedema of the legs and face was noticed. The urine was diminished. For one day there was anuria.

On admission, nearly two months later, there was anasarca and oliguria. The urine contained 12 grams of albumin per liter, white blood cells and casts. No red blood cells were seen. The phthalein excretion was 69% in 2 hours. There was a nasal discharge. The tonsils were swollen and looked inflamed. The leukocytes were 13,000 per c.mm. For three days there was high, unexplained fever, 100–104°F.

During the next three months the albuminuria varied from 2 to 11 grams per liter, and the degree of oedema was variable. On one occasion a few red blood cells were found in the urine. The temperature was often elevated to 100°F., and occasionally rose to 101° or 102°F., without explanation.

On June the tenth the temperature suddenly went up to 103°F. The throat was found to be injected, one ear-drum was inflamed, and signs of peritonitis developed. A precipitin test on the urine was positive for Type I Pneumococcus. An erythematous rash appeared on the face and chest. For 17 days there was a high, continuous fever, 102°–103°F. During this time the albumin in the urine slowly diminished, from 6 grams per liter to a trace, and the oedema disappeared. On the 17th day of fever one ear-drum was punctured and pus escaped (no cultures). During the following week the temperature came down by lysis to normal

For nearly three months there was no oedema. The urine contained at most $\frac{1}{8}$ gram of albumin per liter. The temperature frequently rose to 100°F. (rectal), and occasionally was found to be as high as 101° without any explanation.

Early in October the signs of an upper respiratory infection, with rhinopharyngitis and some cough developed. Two days later oedema reappeared and became generalized. There was slight fever, 100°F., and the leukocytes were 17,000 per c.mm. The urine contained 4.5 grams of albumin per liter, many casts, and a few leukocytes. No red blood cells were found. During the next 17 days all of the signs and symptoms decreased. The temperature was normal or subnormal. Slight albuminuria and oedema remained. She was sent home, and seemed well until the end of December when oedema reappeared and gradually became very extensive. On February 16th, 1923, she was again brought to the hospital with anasarca, high fever, 100°–105°F., and leukocytosis of 38,200 per c.mm. The throat was injected, the tonsils enlarged, red and ragged. In a few hours she had a convulsion, became comatose, and died 36 hours later, with signs of pneumonia. No urine was obtained. *Blood:* Haemoglobin, 64% on last admission. Non-protein nitrogen, 30 mgm. % on last admission. Wassermann negative. *Blood-pressure:* 105/58 mm. of mercury on the last admission. Previously, 112/82 to 100/78. *Spinal Fluid:* Negative.

Autopsy No. 7362. Anatomical Diagnosis: Lipoid nephrosis; generalized oedema; ascites; lobular pneumonia; ulcer, right thigh; fibrous pleural and abdominal adhesions.

Summary of Gross Anatomical Lesions: External Appearance: Marked generalized oedema. An ulcer, 2 cm. in diameter, was found on the medial surface of the right thigh, surrounded by a movable area of induration in the subcutaneous

tissues, several centimetres in diameter, (no sections were made). *Pleural and Pericardial Cavities:* Each pleural cavity contained 25–30 cc. of clear fluid. In the pericardial sac there were 102 cc. *Abdominal Cavity:* Contained 750 cc. of clear fluid. There were oedematous fibrous adhesions about the spleen. *Heart:* Weight, 70 grams. Not enlarged. One small yellow plaque in the base of the mitral valve. *Lungs:* Small scattered patches of lobular pneumonia in each. *Liver:* Periportal tissue pale, yellow, and opaque. *Cranial Sinuses and Ears:* Not examined. *Kidneys:* Weight, 95 and 110 grams respectively. Swollen and pale. Surfaces smooth except for scattered areas, 2–3 mm. in diameter, which were slightly depressed, gray and translucent. Cortex, 6–8 mm. thick, swollen and yellow, in contrast to red pyramids. In the cortex on section there were scattered gray, translucent streaks.

Summary of Microscopical Lesions: Tonsils: Microscopical sections made of one tonsil show diffuse hyperaemia of the tissue. The crypts contain large masses of bacteria, Gram-positive cocci, and diffusely scattered Gram-positive diplococci, together with a purulent exudate. The epithelium lining the crypts is diffusely infiltrated with leukocytes, and in places there are small ulcerations where leukocytes extend for a short distance into the lymphoid tissue. *Lung:* There is a fresh lobular pneumonia, where the exudate consists of red blood cells, leukocytes, and fibrin. A few Gram-positive diplococci can be stained in the exudate. No other organisms are seen. In other areas some of the bronchioles are partly filled with older organizing exudate. Associated alveoli contain purulent and sometimes organizing exudate. *Peritoneal Surfaces and Retroperitoneal Tissue:* In the capsule of the spleen and in the loose splenic adhesions, in the serosa of the intestine, in the capsule and connective tissue and fat about the adrenal, there are small numbers of plasma cells and lymphocytes, with occasional polymorphonuclear leukocytes, often in clumps about small blood vessels. Such chronic inflammatory reaction is especially marked in the septa between the lobules of the pancreas, and in the loose tissue about the pancreas and some small lymph nodes attached. It may be the result of the peritonitis which occurred eight months before death. *Liver:* Each lobule is sharply outlined by a wide zone of liver cells loaded with fat globules. The other liver cells contain small numbers of similar globules of neutral fat (Scharlach R). There is much more fat in the liver than in the kidneys. The Kupffer cells in a wide zone around each central vein are deeply pigmented with haemosiderin. *Adrenal:* In the cortex there are a good many scattered minute areas of freshly necrotic cells. *Spleen:* Phagocytes containing red blood cells and iron pigment are scattered throughout the pulp in moderate numbers. *Bone-marrow:* (Rib) Normal. *Kidneys:* Throughout the cortex there are fairly numerous long narrow scars, one to three in each low-power microscopical field, parallel to each other and to the tubules. These areas contain a few glomeruli in various stages of hyaline scarring and some very small atrophic glomeruli without any hyalinization. Some of the glomeruli are completely scarred and surrounded by thick capsules composed of reduplicated layers of scar

tissue. The tubules in these areas are atrophied. A good many contain small masses of calcified material, and there are some calcified masses between some of the atrophied tubules. A few of the tubules in the areas of scarring contain necrotic cells and show flat lining cells with the usual staining characteristics which indicate regenerated epithelium. The scarred glomeruli and atrophied tubules, and the tissue between are infiltrated with fat. *Glomeruli:* The glomeruli outside the areas of scarring look essentially normal in structure. A few contain small clumps of fat droplets within the epithelium of Bowman's capsule. There are no definite adhesions. No necrotic or regenerating glomerular epithelium can be found. No definite abnormalities are found in the glomerular capillaries in sections stained with haematoxylin and with McGregor's connective-tissue stain. *Tubules:* The convoluted tubules are moderately dilated. The segments most affected in this way are located in the usual place, *i.e.*, deep in the cortex and in the cortical rays. These tubules contain granular débris and very few casts. Most of the epithelial cells show little more than cloudy swelling. Only a few are flattened at all. Only two small haemorrhages are found in tubules in four sections. In frozen sections considerable amounts of fat are found in a good many tubules in each cortical labyrinth. There are, however, quite numerous convoluted tubules in each labyrinth with little or no fat, and the spiral segments and collecting tubules in the cortical rays contain very little fat, as in the kidneys already described. There are numerous collections of fat between these tubules, sometimes forming large masses. Under the polarizing microscope, many typical doubly refractile fluid crystals with Maltese crosses were found at the time of autopsy. Some of the loops of Henle and a few collecting tubules in the medulla contain small numbers of neutral fat droplets in the epithelial cells. *Interstitial Tissue:* There is no oedema of the interstitial tissue, and the blood vessels look normal.

Case 9. J. C., colored boy, 3 years old. Admitted to the hospital on December 5th, 1928. Died on May 19th, 1929. Duration of the disease, one year and six months.

History: The disease began in November 1927, with a "cold," followed by swelling of the face. After that, for a year, generalized oedema was more or less constantly present, disappearing for only a few days now and then. From time to time there was some fever. Fluid was removed from the abdomen on several occasions. No history of peritonitis could be obtained.

On admission to the hospital there was massive oedema with ascites, fever, 106°F., leukocytosis, 42,000 per c.mm., and secondary anaemia. The haemoglobin was 50%. The fever persisted for four days, and was unexplained. The lungs were clear and there was no clinical evidence of peritonitis.

For the next 5½ months the disease was characterized by fluctuating degrees of albuminuria and oedema, periodic fever, sometimes accompanied by diarrhoea, and persistent anaemia.

In January there was fever with pharyngitis, and an X-ray diagnosis of pan-

sinusitis was made. For five days the temperature usually ranged from 101° to 104°F. Albuminuria and oedema were more or less stationary.

On May 11th signs of peritonitis appeared. The temperature rose to 103° and above, and remained elevated for nine days, until death. During this time the albumin in the urine decreased from 9 to 1.5 per liter, and the oedema almost disappeared entirely. An erysipelatoid inflammation developed in the tissues of one leg. *Temperature:* The child was in the hospital for 24 weeks. Some degree of fever was present on at least one day each week for 20 weeks, excluding a febrile reaction from blood transfusion, and the fever associated with the terminal peritonitis. *Urine:* Variable in volume. Oliguria at times. Albumin usually from 5 to 10 grams per liter. Sediment contained many casts at times, and a few white blood cells. Occasional red blood cells were seen on five examinations. *Blood:* Wassermann negative. Haemoglobin, 70 to 50%, in spite of three transfusions. Red blood cells, 2,850,000 per c.mm., when the haemoglobin was 58%. White blood cells, 13,000 to 42,000 per c.mm. *Blood Chemistry:* Non-protein nitrogen, 25 to 31 mgm. %. Total proteins, 3.27 to 4.2 grams %. A/G ratio 17/83 (one determination). Cholesterol 162 mgm. % (one determination). *Blood-pressure:* 95/60 mm. of mercury (one determination).

Autopsy No. 10917. Anatomical Diagnosis: Lipoid nephrosis; slight generalized oedema; encapsulated abscesses between descending colon and right kidney, and in region of splenic flexure; fresh fibrinopurulent peritonitis, and cellulitis of subcutaneous tissues of left foot (Pneumococcus Type II); lobular pneumonia; purulent tonsillitis.

Summary of Gross Anatomical Lesions: External Appearance: Slight oedema of skin and subcutaneous tissues everywhere. Skin loose and wrinkled. *Pleural Cavities:* 10 cc. of clear fluid in each. Fibrous adhesions at left base. *Abdominal Cavity:* Coils of small intestine glued together by fibrinopurulent exudate. A large abscess cavity, 5–6 cm. in diameter, with thick fibrous walls, filled with thick greenish pus, was found between the ascending colon and right kidney. A similar abscess was found behind the colon at the splenic flexure, 2–3 cm. in diameter. *Heart:* Weight, 60 grams. Not enlarged. *Lungs:* Patches of confluent lobular pneumonia in lower lobes. *Liver:* Periportal tissue yellow. *Kidneys:* Weight, 100 and 140 grams. Greatly swollen, pale, yellowish-white. Surfaces smooth. Cortex pale, very thick. Pyramids dark. *Tonsils:* The crypts contain purulent exudate. *Cranial Sinuses and Ears:* Not examined.

Summary of Microscopical Lesions: Tonsils: The surface epithelium is intact. The crypts contain some very large colonies of Gram-positive cocci and numerous scattered Gram-positive diplococci, together with some purulent exudate. The cells of the lining expithelium are spread apart by many infiltrating leukocytes, mostly lymphocytes, and a few polymorphonuclear leukocytes. *Subcutaneous Tissue of Foot:* No microscopical sections were made. Pneumococci, Type II, were cultured from the affected area at autopsy. *Lungs:* There are confluent patches of fresh lobular pneumonia. The exudate contains many red blood cells

together with fibrin and leukocytes. *Retrocaecal Abscesses:* The wall of one of the abscesses is about 2 mm. thick, composed of vascular connective tissue continuous with the serosa of the intestine. On the inner surface there is a purulent exudate. Beneath this lies an organizing layer of fibrin, and below this layer the fibrous wall of the abscess shows a dense chronic perivascular inflammation with lymphocytes. *Pancreas:* In association with the fresh peritonitis the pancreas is oedematous. The acini are spread apart by fluid. Many acini are dilated. There are scattered areas of recent fat necrosis, some associated with collections of fibrinous exudate and a few leukocytes. There are also older areas of fat necrosis in and about the pancreas. Some are encapsulated and contain large phagocytic cells full of fat and masses of calcified material. Throughout the pancreas in all of the septa there is a dense perivascular chronic inflammation with lymphocytes. This chronic inflammation and the old fat necroses may be the result of a former peritonitis which was probably present at the time of admission to the hospital, 5½ months before death. *Liver:* Every lobule is surrounded by a broad band of liver cells which are distended with globules of neutral fat. The other liver cells are somewhat atrophied. There is fat in the Kupffer cells and many of them are deeply pigmented with haemosiderin. *Spleen:* In the pulp and sinuses, phagocytes filled with red blood cells and haemosiderin are found in large numbers. The germinal centres contain a few cells filled with globules of neutral fat. Segments of the walls of some of the arterioles are hyaline, and in fat stains these portions are diffusely infiltrated with fat. *Bone-marrow* (Vertebra): Normal. *Kidneys:* Throughout the cortex there are a few small focal scars, rather narrow and long, containing a few partly or completely hyalinized glomeruli surrounded by atrophied tubules. These focal scars are infiltrated with lymphocytes, and contain some fat.

The upper third of the cortex shows very extensive diffuse *interstitial* scarring. Most of the tubules in this layer are somewhat atrophied, separated from each other by scar tissue, and lined with flattened epithelium.

The glomeruli in this scarred layer of the cortex, excluding those in the focal scars, all look practically normal in structure. They are not smaller than normal. In some a few cells contain clumps of fat droplets. Rarely a small point of adhesion can be found between the cells covering a capillary tuft and the epithelium of the parietal layer of the capsule. The glomerular capillaries are not occluded, nor are their walls apparently thickened. Many capillaries seem to be empty, without any red blood cells. The number of glomerular nuclei does not seem abnormal. There is no inflammation of the glomeruli, and no crescents are found.

In the lower two-thirds of the cortex, excluding the focal scars, the glomeruli look essentially normal, quite like those just described. Most of the convoluted tubules however, show the most extreme degree of dilatation and irregularity in contour. These tubules are lined with flattened cells showing a densely stained pink or purplish cytoplasm. They contain numerous large clear vacuoles, but there is comparatively little evidence of granules in the cytoplasm. A few of the

cells are necrotic. There is practically no calcification of cells, and the cytoplasm of only a few shows "colloid" droplets. A few tubules contain casts. No hemorrhages are found in seven sections. In these deeper parts of the cortex there is a patchy interstitial scarring.

The epithelium of most of the dilated tubules and of many of the atrophied ones is distended with fat, and there are large masses of fat between tubules in the interstitial tissue. In frozen sections and smears there are many doubly refractile fluid lipoid crystals exhibiting typical Maltese crosses. In the medulla a few collecting tubules contain hyaline casts, and there is some interstitial scarring. The arteries and arterioles look normal.

Case 10. E. W., white boy, 10 years old. Admitted to the hospital on November 30th, 1925. Died on May 5th, 1927. Duration of the disease, one year and ten months.

History: In July, 1925, for a week there was severe, cramp-like, abdominal pain, followed by swelling of the face. Gradually, over a period of 5 months, the oedema became generalized. For a week before admission to the hospital moderate abdominal pain was present.

On admission the clinical signs of nephrosis were present, *i.e.*, anasarca, albuminuria, 5.5 grams per liter, normal phthalein excretion, 82% in 2 hours, and normal blood non-protein nitrogen, 38 mgm. %. The urine contained many hyaline and granular casts. No red blood cells were seen. The blood pressure was 120/85 mm. of mercury. The blood Wassermann was negative. The haemoglobin was 95%. There was slight fever, 100°F., and x-ray plates showed clouding of the antra.

On the day after admission the temperature rose to 103°F., the leukocytes to 22,000 per c.mm. Signs of peritonitis appeared. The abdomen was opened and drained. Pneumococcus Type II was grown from the exudate. The signs of peritonitis with high fever persisted for 10 days. During this time the oedema nearly disappeared. By the middle of December there was slight oedema, and the albuminuria had decreased to 2.5 grams per liter. For the next 3 weeks there was a low-grade continuous fever, 100°F., with occasional rise to 101°F., and oedema gradually increased. In January there was high fever, 101–103°F., with leukocytosis, 24,000 per c.mm., and signs of peritonitis were present for three days. At this time the oedema decreased again. The child lost 5 lbs. in weight in three days. The antra were still cloudy (x-ray), and at the end of January one antrum was irrigated once.

For the next 3½ months the degree of albuminuria and oedema was variable. There was a nearly constant low-grade fever, often 100°F., with an occasional rise to 101°. For 24 hours at the end of April there were signs of transient peritonitis with high fever, 103°F. He was sent home on May 13th, 1926, somewhat improved, but still oedematous. *Temperature:* During 24 weeks in the hospital some degree of fever was present on one or more days each week for 21 weeks.

Urine: No red blood cells were seen. *Blood Chemistry:* Non-protein nitrogen, 23–38 mgm. %. Total proteins, 3.88 grams %. A/G ratio 18/82. Cholesterol 420 mgm. %.

One month later, on June 15th, 1926, he was readmitted with moderate generalized oedema, albuminuria, 7 grams per liter, red throat, fever, 103°F., leukocytosis, 21,000 per c.mm., and signs of peritonitis which came on suddenly with cramp-like pain, and persisted for three days. He was sent home again, but continued to have some oedema and albuminuria.

On July 16th he was again admitted to the hospital with marked generalized oedema and albuminuria, 3 grams per liter, slight fever, 100°F., leukocytosis, 10,000 per c.mm., and anaemia. The haemoglobin was 75%. He remained in the hospital for 8 weeks, improved somewhat, but ran a pretty constant low-grade fever, 100°F., at times on several days of seven weeks. For 12 hours on August 26th there was high fever, 100–105°F., without any explanation.

For six months, September 10th, 1926 to March 14th, 1927, he was seen occasionally in the dispensary, with slight oedema and albuminuria. In March massive oedema reappeared and he was again brought to the hospital, with anasarca, 2.5 grams of albumin per liter of urine, anaemia (haemoglobin 66%), and fever, 101°F. The x-ray showed a pansinusitis, and on the third day the antra were irrigated (no cultures). For 12 days there was an irregular fever, 99–103°F. The oedema decreased and the albuminuria diminished from 2.5 grams to 0.4 gram per liter. For the next month, until April 29th, the amount of oedema was variable, but the albuminuria gradually increased to 7 grams per liter, and there was a pretty constant low-grade fever, often 100°F., with occasional elevations of 101°F. He was sent home on April 29th, 1927. A day or so later symptoms of peritonitis reappeared and he died at home on May 5th, 1927. *Blood Chemistry:* (Last admission): Non-protein nitrogen, 19 mgm. % Total proteins 3.96 grams %. Cholesterol, 457 mgm. %. *Blood:* Haemoglogin, 95 to 66%. Wassermann negative (last admission). *Blood-pressure:* 120/85, 105/65, 110/74, 102/64, 114/70 mm. of mercury. *Urine:* Contained a few red blood cells occasionally during last admission.

Autopsy No. 9841: Anatomical Diagnosis: Lipoid nephrosis; generalized oedema; seropurulent peritonitis and lobular pneumonia.

Summary of Gross Anatomical Lesions: External Appearance: Well marked generalized oedema. *Pleural Cavities:* Each contained about 100 cc. of clear fluid. *Abdominal Cavity:* Contained about 200 cc. of thin cloudy fluid. *Heart:* Weight, 140 grams. Not enlarged. *Lungs:* A few small patches of consolidation were found in each lung. *Liver:* The cut surface was mottled with irregular pale areas. *Spleen:* Enlarged. Weight, 120 grams. Pulp everted. *Cranial Sinuses and Ears:* Not examined. *Tonsils:* Not carefully examined. No sections made. *Kidneys:* Very greatly enlarged. Weight, 185 and 215 grams. Surfaces smooth, pale yellowish-white, flecked with minute bright yellow points. A few scattered minute haemorrhages were seen. Cortex, 1 cm. thick. Striations

straight and opaque. *Bacterial Cultures:* In this case the child died at home and cultures were made at autopsy two days later. Streptococci were cultured from the heart's blood. Microscopically, in the tissues, both large Gram-positive diplococci, and chains of smaller Gram-positive cocci are found.

Summary of Microscopical Lesions: In a few bronchioles there is fresh purulent exudate, and in the sections of the lungs a few minute patches of lobular pneumonia are present in which there are Gram-positive diplococci surrounded by clear halos (capsules), and cocci in chains. *Abdominal Connective Tissue:* In the mesentery, serosa of the intestines, and in the loose connective tissue and fat about the pancreas and adrenal, one sees the acute inflammation associated with the peritonitis. In the septa of the pancreas and in the connective tissue about it there are numerous irregular foci of necrosis with fibrinopurulent exudate and numerous Gram-positive diplococci. These same tissues show also focal perivascular accumulations of lymphocytes and plasma cells, probably the result of the repeated attacks of peritonitis described in the history. *Liver:* The liver cells in a narrow zone around each portal space contain moderate numbers of fat droplets (Scharlach R). In a few of the other liver cells there is some finely divided fat in the form of minute granules. Many Kupffer cells contain larger fat droplets. There is no haemosiderin in the liver cells or Kupffer cells. *Spleen:* There are many clumps of cells characteristic of the acute splenic tumor, along with moderate numbers of phagocytes containing red blood cells and haemosiderin granules. *Bone-marrow:* The femur marrow obtained at autopsy is composed of fat. The marrow of one rib examined is normal. *Kidneys:* In the cortex at widely separated intervals there are a few elongated focal scars which consist of several atrophied or partly hyalinized glomeruli surrounded by atrophied tubules. The scars are infiltrated with a few lymphocytes.

The rest of the glomeruli look practically normal in structure. Some contain tufts of capillaries which look empty. The walls of capillaries filled with blood are thin and delicate. In most glomeruli there are a few epithelial cells with small globules of fat. No adhesions are found and there is no evidence of necrosis of the epithelial cells. An occasional glomerular capillary contains a fresh fibrin thrombus. No haemorrhages are found in four sections of the kidneys, although a few were seen in the gross. There is no oedema of the interstitial tissue and the blood vessels look normal.

The convoluted tubules in the cortex are moderately and nearly uniformly widened. There are practically no casts. Some tubules contain a little granular débris. The epithelium of some of the convoluted tubules is a little flattened, but in most of them the cells show cloudy swelling. Practically no necrotic cells are found, and there is no calcification.

In each cortical labyrinth the epithelial cells of a good many tubules are filled with fat, and between the fat-laden tubules there are numerous large masses of fat in the interstitial spaces. Some of the fat is within large phagocytes. In frozen section, under the polarizing microscope, about half of the fat is in the

form of doubly refractile fluid lipoid crystals with Maltese crosses. The rest is neutral fat.

The collecting tubules, and the spiral segments of the proximal convoluted tubules in the cortical rays contain practically no fat. In the medulla the epithelium of most of the loops of Henle and the cells lining many of the collecting tubules contain numerous globules of neutral fat.

2. ON SOME OF THE CHARACTERISTICS OF LIPOID NEPHROSIS

We are not concerned here with the so-called nephrosis of pregnancy, with amyloid nephrosis, or with the relation of syphilis to some examples of nephrosis. The disease in question occurs most often in children, and the following data relate only to the malady first emphasized as *lipoid nephrosis* by Munk (5), *genuine nephrosis* by Volhard and Fahr (6), and *glomerulonephrosis* by Fahr (7). Clausen has used the term *parenchymatous nephritis* (8), and Davison and Salinger suggested *tubular nephritis* in preference to nephrosis (9).

After long discussion and controversy the clinical signs and symptoms peculiar to lipoid nephrosis and the morphological appearance of the kidneys are well known. Everyone is agreed that the urine contains large quantities of albumin without exhibiting macroscopic blood; that the protein content of the blood plasma is lowered, with alteration in the relative proportion of albumin and globulin; that lipaemia is usually present; that there is neither marked elevation of the blood pressure nor hypertrophy of the heart; and that in spite of the pallor of patients with the disease, there may be no apparent anaemia in some cases.

It is also well-known to all that grossly the kidneys are enlarged, soft and yellow, without showing diffuse scarring. The most obvious histological changes concern the convoluted tubules, which look dilated and contain quantities of fat within certain epithelial cells, part of the fat consisting of fluid crystals of doubly refractile cholesterol esters in the form of Maltese crosses when viewed under the polarizing microscope, after heating and cooling. Many authors agree that the glomeruli look relatively normal.

Lipoid nephrosis, however, has been rigidly defined, and in spite of the notorious variability in the manifestations of disease of known etiology and clear pathogenesis, nephrosis is hedged in by criteria and rules not to be violated. The criteria are both clinical and morpho-

logical in character. It is said to be a chronic disease with insidious onset, and clinically it is required that no abnormal number of red blood cells ever appear in the urine, that the blood-pressure remain perfectly normal at all times, and that the patients show waxy pallor without anaemia. Morphologically, the renal tubules must be "degenerated," the glomeruli must look normal, and there can be no abnormal peripheral arteriosclerosis. Indeed, it is said that the kidneys are the only organs in the body which show significant changes (10). Formerly, low basal metabolism and retention of salt were considered to be characteristic features of nephrosis. The mechanism responsible for the low rate of metabolism, when it exists, is not clear, and now it is agreed that this abnormality is not an essential characteristic of the disease (11). As for salt metabolism, it appears that in any form of nephritis retention of salt is in some way associated with the development of oedema, and is not primarily related to the ability of the kidney to excrete sodium chloride (12).

Since there is still doubt concerning many aspects of the disease, it is necessary to examine carefully certain manifestations, both clinical and anatomical, which have given rise to conflicting opinions and to no little confusion in the literature. The data to be presented in the following pages support certain conceptions of the nature and pathogenesis of nephrosis which may be summed up as follows: (1) There is little justification for the assertion that nephrosis is a chronic disease with insidious onset, characterized by remissions and exacerbations, nor for the current idea, often expressed in the literature, that if either anaemia, haematuria, or any elevation of the blood pressure is found, the disease under consideration is not lipoid nephrosis. (2) The demonstrable changes in the kidney consist chiefly of diffuse lesions of the tubular and glomerular epithelium, varying from cloudy swelling to actual necrosis and regeneration. There may also be slight histological evidence of damage to the glomerular capillaries, consisting of small numbers of haemorrhages, capillary thrombi, and of occasional glomeruli in various stages of scarring. The interstitial connective tissue is often oedematous, and in chronic cases may also be scarred. (3) Deposits of neutral fat are usually found in organs other than the kidneys, and their significance is unknown, whether in the kidneys or in other tissues. (4) The non-protein nitrogen of the

blood may be low, normal, or increased at times, but is not constantly or progressively elevated. (5) The blood cholesterol is usually high, but cases are on record in which the cholesterol content of the blood plasma was not increased during active stages of the disease. (6) There is evidence that widespread capillary damage, with escape of albumin from the blood into the tissue spaces, is of considerable importance in the pathogenesis of oedema in nephrosis. (7) There is ample bacteriological, clinical, and histological evidence which reveals a close aetiological relation between some examples of lipoid nephrosis and chronic pneumococcal infection.

(*a*) *Duration*

It is well known, and has usually been unduly emphasized, that nephrosis is often a chronic disease marked by remissions and recurrences. The acute cases of rapid progression and short duration, like those described above, three and four weeks in duration, and other similar examples reported in the literature are identical in every significant respect, both anatomically and clinically, except in duration, with the cases which run a protracted course with remissions and exacerbations. It is important to emphasize the occurrence of acute cases, for those are often associated in a striking manner with clinical signs and symptoms of acute bacterial infection from the onset and throughout the course of the disease. Thorough bacteriological studies of these cases during life, and careful search at autopsy for evidence of foci of infection in the throat, middle ears, and cranial sinuses, are necessary in order to establish the rôle of infection with particular bacteria in the pathogenesis of the disease in each instance.

(*b*) *Anaemia and Urobilinuria*

Although lipoid nephrosis is most often seen in children, the idea that it is not accompanied by anaemia depends to some extent on the results of studies of the blood of adults with the disease. Leiter (13) points out that the data are incomplete, and refers to the studies of Wilbur and Brown (14) as evidence that, in spite of the pallor, actual blood counts and haemoglobin determinations are likely to be normal.

From the mean values and extreme variations found in the red blood cells and haemoglobin values in twenty-five cases of "pure" nephrosis,

Wilbur and Brown concluded that the disease was marked by a striking absence of anaemia. Only two of these cases occurred in children, however, and since anaemia in children with nephrosis had previously been described by Davison and Salinger (9) and by Clausen (15), Wilbur and Brown attempted to explain the discrepancy between the absence of anaemia in adults and its presence in some children by assuming that the cases with anaemia either failed to fulfill the criteria for pure nephrosis, or were complicated by bacterial infection causing the anaemia. Now it is well known that infants and children are readily made anaemic by bacterial infection. Since it is probable that albuminuria and the other manifestations of nephrosis are the result of chronic bacterial infection, it seems likely that anaemia may also be a part of the disease, caused by the same agent.

In 6 of the 10 examples of nephrosis described above anaemia was present during some period of the disease. The blood was not studied frequently in most of the cases, and in one there is no record of haemoglobin or red blood cell count. In the cases in which anaemia was present, the haemoglobin varied from 50 to 66%, and in most of these the anaemia progressed throughout the course of the disease.

It has not been possible to make thorough studies of the bone-marrow in these cases. There are microscopical sections, usually of ribs, in five of them. In these the marrow is apparently normal.

In nine of the cases there is histological evidence of abnormal destruction of circulating red blood cells, *i.e.*, the presence of phagocytosis of the latter by mononuclear cells in the spleen, and pigmentation of the spleen and Kupffer cells of the liver with haemosiderin. In several cases, too, the presence of slight pigmentation of some of the tubules of the kidneys with haemosiderin has the same significance.

The typical color of the urine in nephrosis, the dirty-brown turbid appearance (16), depends, according to Volhard, on pigmentation with urobilin (17), which suggests active blood destruction.

These data, therefore, show that considerable anaemia does exist in some cases of lipoid nephrosis in children. The pigmentation of the tissues with haemosiderin and the presence of excessive amounts of urobilin in the urine suggest that the anaemia is the result of haemolytic destruction of red blood cells, independent of any affection of the bone-marrow. Although the blood bilirubin and the excretion of

urobilin in the stools was not investigated in these cases, the experiments described in the following section show clearly that pneumococcal toxin is a potent haemolytic agent (43).

(c) *The Blood Pressure*

It is generally agreed that in nephrosis there is no persistent hypertension, and inflexible rules have been laid down governing the blood pressure. Nevertheless, the opinions of various authors are not in strict agreement. Leiter states that "neither early nor late in the clinical course of uncomplicated[2] nephrosis is an increase in blood-pressure ever found" (18). Holt and McIntosh say that the blood-pressure is usually normal (19). In four of Davison's cases there were transient periods of elevated blood-pressure (9). As a matter of fact, careful observations on the blood-pressure of children with nephrosis over long periods of time have not been published. There is actually, therefore, no accurate information concerning the *variations* in blood-pressure which may occur.

The blood-pressure was not carefully investigated in most of the ten cases which are reported here. It appears that in some of these cases both the systolic and diastolic pressure were distinctly above normal at times (20). In four cases the systolic pressure was occasionally as much as 20 mm. of mercury above normal, and in three there were times when the diastolic pressure was abnormal, being elevated in one child on a single occasion, as far as the records show, to 100 mm. of mercury. These slight deviations indicate a greater variation in the blood-pressure of children with nephrosis than is generally supposed to occur, and certainly are of importance in showing that some elevation of the pressure can occur from time to time in "pure" lipoid nephrosis. It is the absence of *continuous, progressive hypertension* that is significant.

[2] The idea of "complicated," and "pure" or "uncomplicated" nephrosis has developed, apparently, because in many cases some manifestation of the disease appears at variance with the rules and criteria set up. When therefore anaemia develops, if the blood-pressure is found to be a little abnormal, or when a few red blood cells are recognized in the urine, these natural phenomena are explained away as "complications," "secondary" manifestations, the result of intercurrent infections, or by assuming that nephritis has been "superimposed" on nephrosis.

(*d*) *Non-protein Nitrogen and Cholesterol of the Blood*

Although the presence of normal blood non-protein nitrogen is often named as one criterion of lipoid nephrosis, it is the absence of increasing or persistent retention of nitrogen that is significant. It seems well established, but may be repeated here, that the non-protein nitrogen may be elevated at times during the course of the disease, as recently described by Leiter, and abnormal amounts may be found in the blood when there is marked oliguria, sudden disappearance of oedema, high protein diet therapy, fever, or any other condition accompanied by an increase of protein metabolism (13).

The cholesterol and other lipoids of the blood plasma are usually elevated in nephrosis, as everyone knows, but it should be pointed out that examples are described in which at times the blood lipoids, as measured by the cholesterol content of the plasma, were normal during oedematous, "nephrotic" stages of the disease. Such examples are contained in the papers of Stepp (21), MacKay and Johnston (22), and Schwarz and Kohn (23). In one case reported here (Case 9), the single determination made showed a normal plasma cholesterol, 162 mgm. %, at a time when oedema, albuminuria of 16 grams per liter, low plasma protein, inverted A/G ratio, and normal blood non-protein nitrogen were all present.

(*e*) *Haematuria*

Epstein states that lipoid nephrosis is characterized by "the absence of any blood in the urine" (24). Leiter too says "a variable number of leukocytes is present, but there are *no erythrocytes*" in the urinary sediment. This statement is qualified to some extent by adding that "erythrocytes should not be found in larger numbers or with greater regularity than in supposedly normal urine" (16).

On the contrary, it can be shown from the original case of lipoid nephrosis described by Munk, Volhard and Fahr, and from numerous other case reports, that abnormal amounts of blood do appear in the urine from time to time, and it seems probable that the demonstration of red blood cells in the urine depends partly on the frequency and care with which fresh specimens are examined.

The first published cases of lipoid nephrosis were described by Munk (5), and they have subsequently been referred to in the literature as

characterized by albuminuria, oedema, lipoiduria, and oliguria. Haematuria might well be added, for the presence of red blood cells in the urine of four of the five cases reported was plainly recorded by Munk. The monograph of Volhard and Fahr, "Die Brightsche Nierenkrankheit," contains the description of two cases of "genuine nephrosis" with autopsy. In one of these the presence of red blood cells in the urinary sediment is mentioned several times, and on one occasion the urine contained "eine reichliche Anzahl von roten Blutkörpern." It is interesting to quote Volhard and Fahr concerning haematuria in nephrosis. "Macroscopically visible blood, which we designate haematuria, is always absent. In rare cases isolated red blood cells are found microscopically" (25). A few years later Fahr reported six new examples of nephrosis (26). In two of these the urine was not mentioned. In one the urine was not examined after the onset of the nephrosis. In Case 4 nothing is said concerning blood in the urine. In Case 6 no blood was found, and in one case the urine contained a few red blood cells.

Four of the cases of lipoid nephrosis discussed by Davison and Salinger (9) showed red blood cells in the urine at times, which was explained on the basis of "secondary involvement of a few of the glomeruli." MacKay and Johnston (22) reported a case of lipoid nephrosis seventeen years in duration. On several occasions while the patient was in two New York hospitals, red blood cells were found in the urine. Since microscopically half of the glomeruli were found in all stages of hyalinization, with adhesions and epithelial proliferation in some, it is not remarkable that blood was found in the urine occasionally (27). Stepp and Petri (28), McElroy (29), and Schwarz and Kohn (30) have all reported cases, considered in other respects typical examples of lipoid nephrosis by Leiter, in which small numbers of red blood cells were found in the urine during the disease. In the opinion of Holt and McIntosh (19), in nephrosis "there are never more than a few transient red blood cells in the urine." In a recent publication Volhard (31) says that the absence of blood, microscopically, is not an absolutely constant feature of nephrosis, and that the renal tubules, in the chronic stage of nephrosis, may contain a few red blood cells.

Red blood cells were excreted in the urine of all of the ten cases of

nephrosis described above. In seven cases small numbers of red cells were found at some examination of routine specimens of urine examined in the usual way, without Addis counts, and in the other three blood was found in some tubules of the kidneys in routine microscopical sections. It may be pointed out that in all forms of nephritis the presence of blood in the urine and the quantity found are not constant, but are characteristically variable. From this feature alone, the inconstant presence of haematuria, it might be argued that in nephritis as well as in nephrosis, haematuria is the result of a secondary complication.

From this evidence it is clear that (1) by the absence of haematuria in nephrosis Volhard and Fahr meant gross haematuria, and (2) that lipoid nephrosis is characterized by the appearance of small numbers of red blood cells in the urine from time to time.

(*f*) *The Lesions in the Kidneys*

The ancient classification of nephritis, and the customary procedure, still in vogue, of labelling each example as either "tubular nephritis" or "glomerulonephritis" are responsible in a way for the confusion in the literature concerning the nature of lipoid nephrosis, the very existence of which has been denied. This classification implies that anatomically, functionally, and with respect to pathological lesions, the glomeruli and tubules are sharply separated. In any case, however, whether of "nephrosis" or "nephritis," there is little justification, anatomically, for the terms "tubular degeneration" or "tubular nephritis" in contrast to "glomerulonephritis," for whenever the tubular epithelium is swollen, fat-laden, necrotic, or regenerating, similar changes are found in the glomerular epithelium, though not always in the same degree. In "glomerulonephritis" although capillary thrombi, haemorrhage, and crescentic masses of exudate are easy to see, the "degenerative" changes are always present in the glomerular and tubular epithelium. Furthermore, physiologically the terms are not only inaccurate but are actually misleading, for in any form of Bright's disease, whether caused by metallic poisons, bacterial toxins, or by arteriosclerosis, the chief functional disorders, the escape of red blood cells and proteins from the blood, and the inability of the kidney to excrete non-protein nitrogen, are pretty clearly dependent chiefly on damage to the glomeruli.

Concerning the glomerular lesions in lipoid nephrosis, everyone is agreed that there may be a few glomeruli in some stage of destruction and replacement by scar tissue. These are usually spoken of as focal scars, since they are generally few in number, unless the disease is very chronic, when scarred glomeruli may be fairly numerous. The tubules connected with the scarred glomeruli are atrophied, and it is said, without any evidence, however, that destruction of the glomeruli is secondary to the changes in the tubules. On the other hand, since damage to the capillaries of some glomeruli sufficient to cause occasional microscopical haematuria does occur in nephrosis, this alone suggests that the presence of small numbers of visibly damaged glomerular tufts might be expected.

In general there are three views regarding the state of the *majority* of the glomeruli in nephrosis. They are described by some as normal. Others find evidence of glomerulonephritis or glomerulitis. A third group describes the glomeruli as showing "degenerative" changes.

In the most recent review of the subject, the opinion is expressed by Leiter (32) that the glomeruli are normal in nephrosis. But it is also said that "the pure uncomplicated type of nephrosis is rare at autopsy. Very frequently there exists in addition a mild chronic glomerulonephritis which has been overlooked clinically" (33). It may be said in this regard that there are no accurate histological, clinical, or other methods for determining that the lesions of chronic glomerulonephritis, however mild, which may be found in a kidney, are present *in addition* to the lesions of some other disease characterized by continued albuminuria. The theory that the glomeruli in nephrosis are normal is based on the idea that if "glomerulitis" or crescents are present, both of which, it may be noted, are *reactions* to injury, the condition under consideration is glomerulonephritis, and that if these lesions are absent, the glomeruli are normal. The evidence of injury, and regeneration of glomerular epithelium, short of epithelial crescent formation, is disregarded. Haemorrhages in tubules, admittedly originating from glomerular capillaries, are either not mentioned or are said to be secondary, but it is never clear to what they are secondary. Thrombi in glomerular capillaries are not mentioned.

As further evidence that the majority of glomeruli are normal in lipoid nephrosis, Leiter (34) states that Fahr also described only focal glomerular lesions, secondary in origin. It is also said that Löhlein,

after a study of Fahr's cases of nephrosis, admitted that the sections showed nothing remotely resembling an old or recent glomerulonephritis. In the papers of both Fahr and Löhlein, however, diffuse lesions of the glomerular capillaries in lipoid nephrosis are described, as clearly shown by the following quotations from these papers.

According to Fahr (7), the glomeruli show "degenerative changes, which, however, in no way affect the tufts equally. In fresh cases, the majority of the glomeruli are unchanged, but in a number of tufts there is widening and swelling of the capillary wall and of the parietal layer of the capsule. There may be adhesions between the two capsular lamellae. The swelling of the capillary loops and the adhesions become more and more obvious in older cases. Hyaline clumping of the capillaries takes place, which reminds one of amyloid degeneration of the glomeruli. . . . . In the main, there are degenerative changes in the glomeruli, in the sense of fat accumulation and hyalinization. These are slight in the beginning, gradually progress, and finally may lead to destruction of the tufts. There is here . . . . not only a tubulonephrosis, but also a glomerulo-nephrosis, and this glomerulo-nephrosis is of the greatest importance for the pathogenesis of this form of nephrosis. Gradually, reactive processes occur, especially in the interstitial tissue, but also in lesser degree in the glomeruli. . . . . The degenerative changes in the tubules and in the glomeruli proceed together in the first place, but as soon as they have reached greater intensity, naturally they can remain no longer without reciprocal influence on each other. Destruction of the glomerulus has a great influence on the destruction of the tubule, and *vice versa.*" In the discussion of subacute glomerulonephritis, Fahr says plainly, "I agree emphatically that the atrophic changes in the tubules in glomerulonephritis, just as in chronic nephrosis, are predominantly dependent on glomerular damage" (35).

Löhlein (36) describes the glomeruli of the examples of nephrosis sent to him by Fahr as follows: "One finds here and there somewhat conspicuous changes in the glomerular tufts. One can also establish, by careful comparisons with sections of normal kidneys, that the capillary walls of the glomeruli throughout appear somewhat altered, as if swollen. Occasionally they contain more cells than normal. In many cases they contain lipoid masses here and there, the capillary epithe-

lium also is somewhat swollen, and contains fat here and there. But it is not proven that all of these findings must be interpreted as the result of an 'infectious glomerulitis,' or 'acute glomerulonephritis.' Here I agree with Fahr in his latest work in which he described the presence of *diffuse* glomerular capillary changes with almost the same words which I have used. . . . . It now seems to me most probable that this diffuse damage has not led to the release of an outspoken inflammatory reaction; in other words, that in the kidneys in question an acute glomerulonephritis has never taken place."

These quotations can leave no doubt that Fahr described diffuse "degenerative" changes in the glomerular tufts which resembled amyloid deposits, and while Löhlein considered the lesions unlike those usually found in acute glomerulonephritis, he plainly stated that he was in agreement with Fahr concerning the presence of *diffuse histological changes* in the glomerular capillaries. It has been suggested by Volhard (31) that the cases described by Fahr represent some other form of nephritis, with more definite histological lesions in the glomerular tufts than are present in nephrosis.

To turn now to the views that in nephrosis the glomeruli show "degenerative" changes or lesions of "glomerulonephritis" or "glomerulitis," the opinion of Fahr and that of Löhlein, that there are diffuse hyaline changes in glomerular capillaries, with thickening of the capillary walls, have been quoted already. Dunn (37) is of the opinion that "close examination of a large number [of glomeruli] always reveals some stigmata of an antecedent glomerulitis." Löwenthal (38) described definite lesions, such as necrosis of the capillary walls and hyalinization of glomeruli with many nuclei. Bell (39) described four cases, considered examples of lipoid nephrosis, and concluded that nephrosis is a form of glomerulonephritis in which there are characteristic changes in the capillaries, thickening of the basement membranes and partial obstruction of the capillaries by an increase in the size and number of endothelial cells.

From careful histological examination of the glomeruli of the ten examples of nephrosis reported above the conclusion is reached that lipoid nephrosis is a form of diffuse nephritis, marked in these cases by the absence of lesions in the glomerular capillaries that are demonstrable anatomically. The variety of glomerular changes found may be

summed up as follows: (1) Diffuse changes in the glomerular epithelium which are identical in nature with the lesions in the tubular epithelium, but differ in degree. Changes identical in kind occur in the glomerular epithelium in "glomerulonephritis." (2) Partly and completely hyalinized, scarred glomeruli, occurring in small numbers and at widely scattered intervals, focal glomerular scars. These are in association with small patches of atrophied tubules. They are identical in appearance with scarred glomeruli which may be found in any form of nephritis, and there is no good evidence that they are secondary in origin to destruction of tubules. (3) Numerous tufts of empty capillaries whose walls look thick compared with capillaries filled with blood. There is no proof that these capillaries are thickened, since similar thick-looking capillaries are found in normal kidneys whose capillary tufts are not filled with blood. (4) There may be haemorrhages in tubules, and there is no evidence that these are different in pathogenesis from the haemorrhages which occur in any form of glomerulonephritis. (5) Thrombi within some glomerular capillaries.

The lesions of the glomerular capillaries described by Fahr, Löhlein, Löwenthal, and Bell are not found in the kidneys of this series of ten cases. The diffuse changes in the epithelial cells, and the obliteration of glomeruli, although the latter occurs in slight degree, are processes which occur in identical form in cases of well recognized glomerulonephritis. Histologically, they differ chiefly in degree in the two diseases, and in recognized glomerulonephritis there are ***in addition*** other more conspicuous lesions, *i.e.*, clots containing fibrin, and perhaps even leukocytes and red blood cells, in many of the capsular spaces and between capillary tufts. These on becoming organized lead to the destruction of numerous glomeruli and often to obstruction of the neck of the proximal convoluted tubules. Obstruction of the mouth of these tubules, even before the exudate is organized, in its freshly clotted state, is obviously of great importance in preventing the normal excretion of urine.

There is more or less general agreement concerning the changes in the tubular epithelium in nephrosis. The convoluted tubules are most affected. It is well known that they show varying degrees of dilatation, and that the epithelial cells may contain neutral fat and

doubly refractile cholesterin esters. Often necrosis of some cells can be recognized, and both calcified necrotic cells and regenerated epithelium may be found. The cytoplasm of some cells forms "colloid" droplets, as evidence of some degree of damage, but many of the cells show nothing more than cloudy swelling.

It is impossible to give an accurate general description of the tubular lesions in lipoid nephrosis, since they are very variable, and differ somewhat in degree in each case. From the study of the kidneys in this series, the following points may be emphasized. (1) The changes in the calibre of affected tubules may be very slight, and the mechanism responsible for this lesion is not clear. There is no good evidence to show that the tubules in the cortex are actually dilated from obstruction of collecting tubules with casts, the usual explanation. (2) In cases of short duration not only all of the convoluted tubules, but also the collecting tubules *in the cortical rays* may be considerably wider than normal, without evidence of obstruction by casts to explain the diffuse dilatation. (3) In acute cases there may be very little demonstrable fat of any kind in the tubular epithelium, and in any case there is as much neutral fat in the kidney as doubly refractile lipoid. (4) In cases of short duration even small numbers of doubly refractile lipoid fluid crystals may be very difficult to demonstrate in the tubular or glomerular epithelium, not only in frozen sections but also in smears from scrapings of the kidney soon after autopsy. (5) The fat in the cortex of the kidneys has a striking radial arrangement and is found for the most part in each *cortical labyrinth* in the epithelium of some but not all of the convoluted tubules, and in the interstitial tissue. The spiral segments of the proximal convoluted tubules, which lie in the *cortical rays*, contain scarcely any fat, although these segments especially are widened, and their epithelium may show marked degrees of cloudy swelling, vacuolization, and even some necrosis. (6) The loops of Henle in the pyramids, and often some of the collecting tubules in the same location, may contain quantities of neutral fat in the epithelium, although these tubules are said to be unaffected. (7) None of these changes in the tubules is specific for lipoid nephrosis, and it is well-known that they occur also in many cases of out-spoken acute and subacute glomerulonephritis. (8) At present there is no functional disorder that can be confidently ascribed to the

changes in the tubules. The most important functional change, albuminuria, is certainly the result of damage to capillaries, obviously those of the glomeruli, which leaves no definite anatomical alteration that can be demonstrated by present histological methods.

Several questions now naturally arise. How may "nephrosis" be differentiated clinically and anatomically from "nephritis?" Are the cases referred to in the literature with widespread histological lesions of glomerular capillaries to be considered examples of nephrosis? Is lipoid nephrosis a distinct entity?

In answer to the first question, it is probable that continued haematuria of considerable degree, the presence of persistently elevated non-protein nitrogen in the blood, or marked decrease in the excretion of phenolsulphonphthalein, may be considered indicative of progressive diffuse destruction of glomerular capillaries and obstruction of the outlet from the glomerular capsules. Massive albuminuria, casts in the urine, and slight haematuria may continue for long periods without the occurrence of diffuse obstruction and destruction of glomeruli. Anatomically, it is the absence of visible changes in the majority of glomerular capillaries, and of clots of exudate within the glomerular capsules, and the absence of excessive regeneration of glomerular epithelium that separates nephrosis as a distinct entity from other forms of nephritis.

Since we do not know as yet how many glomeruli may be in part or completely obstructed and destroyed before the normal excretion of non-protein nitrogen, for example, is impaired, it is impossible, in the absence of chemical studies, to say that some cases described in the literature with diffuse histological lesions of the glomerular capillaries were not at least clinical examples of nephrosis in many respects. It is obvious, however, as Leiter has pointed out, that the cases described by Bell (39) do not fall into the group under consideration here as lipoid nephrosis, for in Case I of his series the phenolsulphonphthalein excretion was only 27%, in Case III 15%, and in Case IV the blood urea was 144 mgm. %.

Lipoid nephrosis seems indeed to be a distinct form of diffuse nephritis with particular clinical and anatomical characteristics. These may persist for long periods, at least in children, without the development of destructive lesions in the majority of the glomerular tufts,

lesions which do progressively multiply during the course of typical subacute and chronic glomerulonephritis. The examples of nephrosis associated with chronic pneumococcal infection appear to be distinctly separate in etiology from many other examples of glomerulonephritis.

(g) *Changes in Other Tissues*

The consensus of opinion expressed in the literature is that the kidneys are the only organs which are appreciably affected, histologically, in lipoid nephrosis. Much emphasis is placed on the presence of fat in the tubular epithelium of the kidneys, and the presence of doubly refractile fluid crystals of cholesterin esters is supposed to be of great importance.

It has already been shown above that the classical signs and symptoms may all be present in acute cases when the renal epithelium may contain minimal amounts of fat, and very few fluid lipoid crystals, demonstrable with difficulty. The lipoids in the kidney can therefore be of little importance in the pathogenesis of either the albuminuria, lipaemia or oedema. What significance they have is uncertain.

Since, however, as the disease becomes more and more chronic, the amount of fat usually increases in the kidneys, it is interesting at least that neutral fat has been described in other organs, although little attention has been given to these changes. Shapiro (40) and Löwenthal (38, 41) reported cases with the description of fat in the liver and spleen especially. In Löwenthal's cases the fat was conspicuous in the periportal liver cells, and he also described fatty deposits in the aorta of two children.

In eight of the ten cases described above fat stains could be made of liver, spleen and pancreas. In the first example of nephrosis, three weeks in duration, there is very little stainable fat in either the liver, spleen, pancreas or kidneys. In the other nine cases, within phagocytes of the spleen, and in acinar epithelium of the pancreas, variable amounts of neutral fat (Scharlach R) are present in each. In the spleen the fat is most abundant in cells of the germinal centres of the Malpighian bodies. In some cases there are numerous fat-laden cells throughout the splenic pulp, and in five of the spleens, segments of the walls of a few of the arterioles are diffusely infiltrated with fat. These arterioles, in the haematoxylin and eosin stains, look hyaline, as in the

ordinary diffuse arteriolosclerosis. In two cases, an occasional hyaline arteriole, infiltrated with fat, can be found in the pancreas.

The livers of these cases all contain neutral fat, both in the Kupffer cells and the liver cells, and in general the amount of fat in the liver parallels that in the kidney. The fat in the liver cells is located especially within a zone around each portal space, and even in cases where cells throughout the lobules contain fat, the periportal cells show more than the others. In some cases the liver contains more fat than the kidneys.

Whether or not the same mechanism is responsible for the presence of fat in the kidney, liver, and other tissues is unknown, nor is it known whether the fat in the cells is an expression of slight damage, is the result of lipaemia, or is caused in some other way.

(*h*) *On the Pathogenesis of Oedema in Nephrosis*

It is generally agreed that in acute nephritis the relatively high percentage of albumin in the oedema fluids and urine indicates capillary damage, while it is denied that this mechanism plays any part in the formation of oedema in nephrosis. Leiter has summarized the evidence concerning the origin of oedema in nephrosis (42) and since the *percentage* of protein may be smaller in the oedema fluids of nephrosis (0.01 to 0.4 gram %) than in the body fluids in acute nephritis (0.39 to 2.52 gm. %), it is argued that if capillary permeability to protein plays any rôle in the formation of oedema in nephrosis, the percentage of protein in the fluid should be higher. It is therefore concluded that oedema in nephrosis is formed largely by mechanical forces (low plasma proteins and low osmotic pressure), and that increased permeability of the body capillaries to the proteins of the blood is not involved in any way.

According to the accepted views regarding the pathogenesis of oedema in nephrosis, when the osmotic pressure exerted by the normal plasma proteins falls below the "filtration pressure," *i.e.*, the blood pressure, because of the excretion of albumin, the "filtration pressure" forces water into the tissue spaces. This is prevented normally by the force of the higher osmotic pressure associated with normal quantities of plasma protein which tends to retain water in the blood plasma.

The mechanical theory of the origin of oedema in nephrosis has cer-

tain defects. It is therefore desirable to tabulate these, and to summarize data which indicate that generalized capillary damage and abnormal permeability to proteins of the plasma are important factors in the pathogenesis of oedema.

(1) First, the mechanical theory of oedema fails to account for the presence of proteins in the fluid. A decrease in the osmotic pressure of the blood from loss of plasma protein in the urine is no doubt an important factor in aiding the accumulation of *fluid* in the tissues and body cavities, but it seems unlikely that it is responsible either for the presence of albumin in the oedema fluids or for that in the urine.

(2) Much emphasis is placed on the presence of relatively low *percentage* of albumin in the oedema fluids of nephrosis, compared with that found in the oedema of acute nephritis. According to Leiter, more than 0.5% protein is not to be expected in nephrosis. This amount, however, is as great as that reported in the oedema fluids of some cases of glomerulonephritis. The presence of proteins in the transudates of nephrosis cannot, therefore, be dismissed simply because the percentage is smaller in some cases than that found in the oedema fluid of some examples of glomerulonephritis.

(3) The oedema fluid of nephrosis is said to be a low protein filtrate of the plasma, "very much like cerebrospinal fluid," formed by mechanical means, without any change in the permeability of the capillary wall to protein (42). The quantity of protein in the normal spinal fluid is said by Starling to be a "mere trace," by Macleod to be a trace (0.02–0.04 *total nitrogen*), and by Howell to be "traces." The oedema fluids of nephrosis, however, often contain a percentage of *protein* (0.1 to 0.4 gm. %), from five to twenty times the total nitrogen found in the normal cerebrospinal fluid (42).

(4) Conclusions concerning capillary permeability based on the *percentage* of protein in oedema fluids may be misleading, since the total amount of protein may be greater in a large volume of fluid with low percentage of albumin than in a smaller volume of fluid with a higher percentage of proteins. This is of some importance, since in acute nephritis with moderate oedema the proteins in the fluid may be concentrated in a small volume of fluid and the percentage therefore high, while the percentage of protein may be low but the total amount high when the protein is diluted in the massive oedema and ascitic fluids which are usually present in nephrosis.

(5) The percentage of protein in oedema fluids cannot be accurately compared at a given time with the percentage of protein in the urine at that time, for the former represents the average percentage of protein which has accumulated and varied over a long period, while the albumin in the urine is carried out in varying concentrations from day to day. Comparisons would be analogous between the percentage of protein escaping through the glomerular capillaries and that passing through the tissue capillaries *at the same time*. Or, the percentage of albumin in ascitic fluid, present for a given period of time, would be analogous to the *average* percentage of albumin in the total volume of urine excreted during the same period. Thus, it may be shown in an experimental animal (R. 34–21, table V) that the percentage of albumin found in ascitic fluid at the end of four days may be practically equal to the *average* percentage content of albumin in the total volume of urine excreted during this time (43). Furthermore, the percentage of albumin in these fluids, 0.2 gm. %, may be within the limits prescribed for protein in the oedema fluids of nephrosis in the human being.

(6) As far as it is known, the albumin in the oedema fluids in nephrosis is identical with that excreted in the urine. This suggests that the same mechanism may be responsible for the presence of albumin in both fluids.

(7) In the presence of hypertension, with or without progressive nephritis, it is possible that the blood pressure within the capillaries may exceed the osmotic pressure excreted by the plasma proteins. Oedema should therefore mechanically follow, according to the theory. The normal capillary blood pressure is generally said to be about 20 mm. of mercury. The normal osmotic pressure of the blood plasma, as given by various investigators, varies from 25 to 33 mm. of mercury. Examples of hypertension *without oedema* have been reported in which the capillary pressure was doubled, 40 mm. of mercury, in the presence of normal and even lowered plasma proteins (44).

(8) Since in experimental pneumococcal nephritis the loss of proteins into tissues and body cavities along with fluid may be one of the *causes* of low plasma protein (R. 55–1, table III, having excreted only 16 cc. of urine with 0.225 gram of albumin, when the plasma protein was low, 3.16 gm. %, and oedema was present), there is reason to

believe that in experimental pneumococcal nephrosis also, produced with relatively small amounts of the same toxin, as well as in nephrosis in man, the albumin found in the oedema fluids, and to this extent oedema itself, is related to widespread capillary damage, with loss of plasma proteins into the tissues as well as in the urine (43).

It is evident that numerous and complex factors are always concerned in the pathogenesis of oedema. The data summarized above indicate that in nephrosis as in other types of nephritis one important factor is capillary damage and abnormal permeability to plasma protein. Neither capillary damage alone, nor mechanical factors alone (low plasma protein and osmotic pressure), nor these two together are sufficient to explain the oedema of nephrosis, for it is a familiar fact that the oedema may decrease or disappear if salt is removed from the diet, despite the presence of albuminuria and persistence of the mechanical forces which are said to be responsible for the occurrence of oedema.

(*i*) *The Relation Between Nephrosis and Bacterial Infection*

The evidence already summarized concerning the physiological and morphological changes in the kidneys in lipoid nephrosis indicates that this disease is a form of nephritis. It follows, therefore, that nephrosis may be similar to nephritis in etiology. It is now well-known that the etiology of glomerulonephritis is usually related to foci of bacterial infection outside the kidneys. The careful clinical and bacteriological studies of Longcope (45) have shown clearly that many cases of acute and chronic glomerulonephritis are associated with streptococcal infections of the nasopharynx and cranial sinuses.

No thorough studies of the relation between nephrosis and bacterial infection have been reported. Clausen (15), Marriott (1), Aldrich (2), Govaerts and Cordier (3), and Schwartz and Kohn (30) have all published cases intimately associated with bacterial infection. Recently Volhard expressed the opinion that chronic infection with Pneumococci is often the cause of "genuine" nephrosis (4). As evidence he describes the course of a number of cases, and concludes that "one must therefore assume an infectious etiology for the supposed 'genuine' nephrosis, and in the future, much more than in the past, attempt to locate a chronic staphylococcal or pneumococcal infection."

The bacteriological studies which were made in the examples of nephrosis included in this paper are incomplete. Clinically, the relation between persistent bacterial infection and the pathogenesis of the disease was not investigated. At autopsy the cranial sinuses were not examined in any of the cases, and in some of them microscopical sections of the tonsils were not made. There is evidence, however, that from the onset and throughout the entire course of the disease in each case, persistent infection with Pneumococci was present.

The ten cases may be conveniently divided into two groups, four cases of short duration, three to seven weeks inclusive, and six cases of chronic nephrosis, five and a half to twenty-two months in duration. Fever was the first symptom noticed in two cases in the first group. It was accompanied by definite signs and symptoms of an acute respiratory infection in one of the two cases, and in each one the presence of oedema was noticed after the onset of fever. There was clinical evidence of upper respiratory infection (pharyngitis, tonsillitis, or otitis) in three of the cases, and in three instances Pneumococci were cultured from the throat. In each of these cases there was leukocytosis, and in three irregular fever was present throughout the course of the disease. Pneumococcal septicaemia and peritonitis developed in each of the four cases, with pneumonia, pleurisy, and pericarditis also in some instances. In one case an abscess developed in the neck, and spreading pneumococcal cellulitis of the chest wall appeared before the onset of peritonitis. Microscopically, in two cases, evidence was found of subacute and chronic pneumococcal infection of the tonsil. The tonsils and pharynx were not examined in the other two cases.

In three of the six examples of chronic nephrosis the disease began with fever, or with other symptoms of infection of the upper respiratory tract. The presence of leukocytosis and continued irregular low grade fever during the course of the disease, and the clinical evidence of pharyngitis and tonsillitis in each case, with, in addition, evidence of chronic sinusitis in two cases, point to the presence of persistent bacterial infection. The development of transient or fatal terminal pneumococcal peritonitis in each case, and the presence of chronic infection of the tonsil with diplococci in the three cases in which the tonsils were examined microscopically, suggest that these persistent chronic infections were caused by Pneumococci. There is

some evidence, in the chronic cases, to indicate the occurrence of repeated unrecognized attacks of peritonitis. In one child, with nephrosis for one year and ten months, five attacks of acute peritonitis were recognized. The abdominal connective tissues in this case show chronic perivascular inflammation, as described above in the protocol. In another case, in addition to similar chronic inflammation in the abdominal connective tissues, two large pneumococcal abscesses were found in the abdominal cavity, encapsulated with walls of scar tissue. Only the terminal acute peritonitis was recognized clinically in this case, however. In each of the other chronic cases there is chronic inflammatory reaction in the abdominal connective tissue. These histological changes, together with the occurrence of short periods of high fever without any obvious explanation clinically, suggest that peritonitis occurred more often than suspected, and that its terminal appearance was not merely an unrelated secondary complication of nephrosis. The well-known fact that the signs and symptoms of nephrosis often disappear with recovery from peritonitis or pneumonia, as in some of the cases described above, suggests that these intense infections produce temporary or even permanent immunity.

The association between nephrosis and bacterial infection has sometimes been explained by assuming that the disease predisposes to infection, or that the fluid-filled tissues afford favorable media for bacterial growth. It is only necessary to point out that in other forms of nephritis, in amyloid nephrosis, in heart failure with anasarca, and in cirrhosis of the liver with oedema and ascites, the tissues and body fluids are not repeatedly invaded and infected with Pneumococci. This alone suggests that in lipoid nephrosis there is some more intimate relation to bacterial infection than a mere predisposition to infection. Especially significant in many of these cases is the continued record of low grade fever and leukocytosis, often in the presence of anasarca, usually unexplained clinically, and pointing to the presence of chronic bacterial infection.

3. CONCLUSIONS

1. Evidence is collected from classical examples of lipoid nephrosis described in the literature and from the study of ten cases in children which shows that nephrosis is a particular form of diffuse nephritis in

which microscopical haematuria, secondary anaemia of haemolytic origin, and slight elevation of the blood pressure may all occur at times as part of the disease.

2. Acute cases of short duration occur without any evidence of "insidious onset." In these the amount of both neutral fats and doubly refractile cholesterol esters in the kidneys may be very meagre.

3. The non-protein nitrogen of the blood may be normal, or above normal at times, but is not constantly or progressively elevated.

4. The histological lesions in the kidneys consist chiefly of certain diffuse changes in the epithelium of the glomeruli and tubules, identical in kind with those which may occur in any form of nephritis. The disease may persist for a long time, at least in children, without the development of other lesions in the majority of the glomeruli.

5. Scarred glomeruli (focal scars) may be found in small numbers, and these also are indistinguishable from scarred glomeruli which are found diffusely in chronic glomerulonephritis. There is no evidence that these focal scars are "secondary" to changes in the tubules.

6. No changes in the glomerular capillaries can be recognized to account for the excretion of albumin in the urine. The most important histological distinction between "nephrosis" and "nephritis" depends on the absence of coagula containing fibrin within the glomerular capsules in nephrosis. In the absence of these clots, organization and scar tissue formation with destruction of glomeruli and progressive renal insufficiency do not occur. The mechanism responsible for the absence of coagula within the glomerular capsules in nephrosis and for their presence in glomerulonephritis has not been fully determined, but seems obviously related to the excretion of fibrinogen in the urine in addition to albumin.

7. In the ten cases of nephrosis described, fat deposits are present in tissues other than the kidneys. In general the amount of fat in the liver parallels that stained in the kidneys. The significance of the fat deposits in the tissues, including the doubly refractile cholesterol esters in the kidney, is entirely unknown. The presence of deposits of neutral fat and cholesterol esters is in no sense specific for lipoid nephrosis. In the kidneys the fat in the epithelium of the tubules of the cortex is found predominantly in segments of the convoluted tubules which lie in each *cortical labyrinth*. Although the epithelial

cells of the tubules in the *cortical rays* show other alterations varying from cloudy swelling to actual necrosis and regeneration, these cells contain scarcely any fat deposits.

8. Data are tabulated which indicate that the oedema of nephrosis cannot be explained by mechanical factors alone. There is good evidence that widespread capillary damage is one important factor in the pathogenesis of oedema in nephrosis.

9. There is no evidence that lipoid nephrosis is a "metabolic" disease, "diabetes albuminuricus." Clinical and pathological data are presented which point to the etiological relation between chronic pneumococcal infection and the pathogenesis of some examples of lipoid nephrosis. This is supported by the experimental reproduction of nephrosis in animals by means of pneumococcal toxin to be described separately.

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EXPLANATION OF ILLUSTRATIONS

(Photographs by Mr. Milton Kougl)

FIG. 1. Case 4, autopsy 12775. Gross kidney, lipoid nephrosis, 7 weeks' duration.

FIG. 2. Case 6, autopsy 10902. Gross kidney, lipoid nephrosis, 7½ months' duration.

FIG. 3. Case 1, autopsy 12205. Gross kidney, lipoid nephrosis, 3 weeks' duration.

FIGS. 4, 5, AND 6. Photomicrographs of sections of the kidneys shown in figs. 1, 2 and 3. There are no demonstrable changes in the walls of the capillaries. The glomerular capsules contain no exudate. The interstitial tissue between the tubules is oedematous (figs. 5 and 6). The calibre of the tubules is accentuated by the thin epithelial lining.

FIG. 7. Case 7, autopsy 12135. Gross kidney, lipoid nephrosis, 9 months' duration.

FIG. 8. Case 9, autopsy 10917. Gross kidney, lipoid nephrosis, 1 year and 6 months' duration.

FIGS. 9 AND 10. Case 3, autopsy 12176. Kidney, lipoid nephrosis, 6 weeks' duration. In the gross the cortex is swollen and pale. Microscopically (fig. 10),

there is some oedema of the interstitial tissues. The convoluted and collecting tubules in the cortex are equally dilated. This appearance depends in part on the thin epithelial lining of the tubules. A few casts are present. The glomerular capsules contain no clots, and the capillaries look normal.

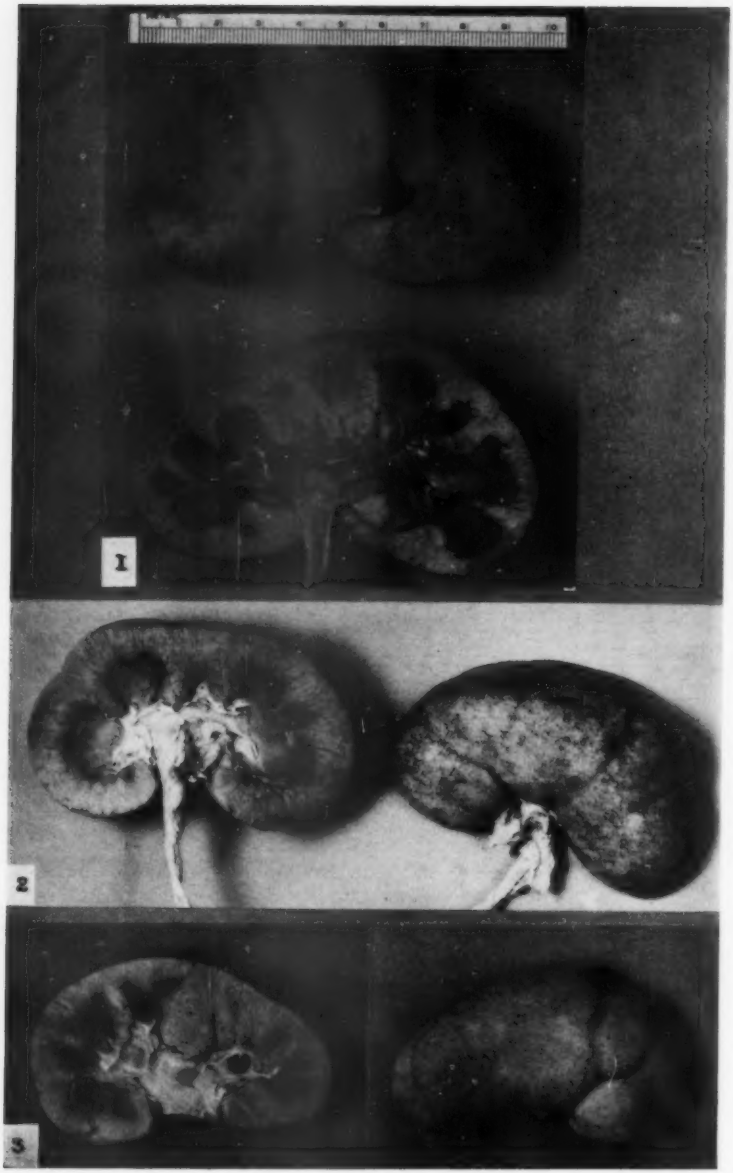
FIG. 11. Photomicrograph of a section of the kidney of case 7 (fig. 7), nephrosis 9 months' in duration. The glomerular capillaries look normal. The capsular spaces contain no recent or organized clots of exudate. The tubules are rather wide, but contain few casts.

FIG. 12. Photomicrograph of the kidney of case 9 (fig. 8), nephrosis 1½ years in duration. Although the tubular striations are distorted by widespread scarring of the tissue between them, the glomerular capillaries look normal, and there are no clots of exudate within the glomerular capsules.

FIGS. 13 AND 14. Case 2, autopsy 9582. Lipoid nephrosis, 1 month in duration. Figure 13 shows what has usually been described as one of the characteristic lesions in lipoid nephrosis, the presence of more marked changes in the convoluted than in the collecting tubules of the cortex. The preceding figures (figs. 5, 6, 10, 11, and 12), however, show that often both convoluted and collecting tubules in the cortex are wide, lined by flat epithelium. In fig. 13 no glomerular lesions can be seen. A higher magnification (fig. 14) shows changes in the glomerular epithelium, however. At "3 o'clock" there is an adhesion formed by a syncytial mass of epithelial cells over a capillary tuft. Two or three of the cells are necrotic, with pyknotic nuclei. The arrows point to other single swollen epithelial cells. The walls of the capillaries look normal. They are not occluded by endothelial cells. The glomerular capsules contain no exudate.

FIGS. 15 AND 16. Frozen sections of liver (Case 8) and kidney (Case 10) stained with haematoxylin and Scharlach red, showing the radial accumulation of fat in the periportal liver cells, and in the interstitial tissue and epithelium of some tubules in each cortical labyrinth.

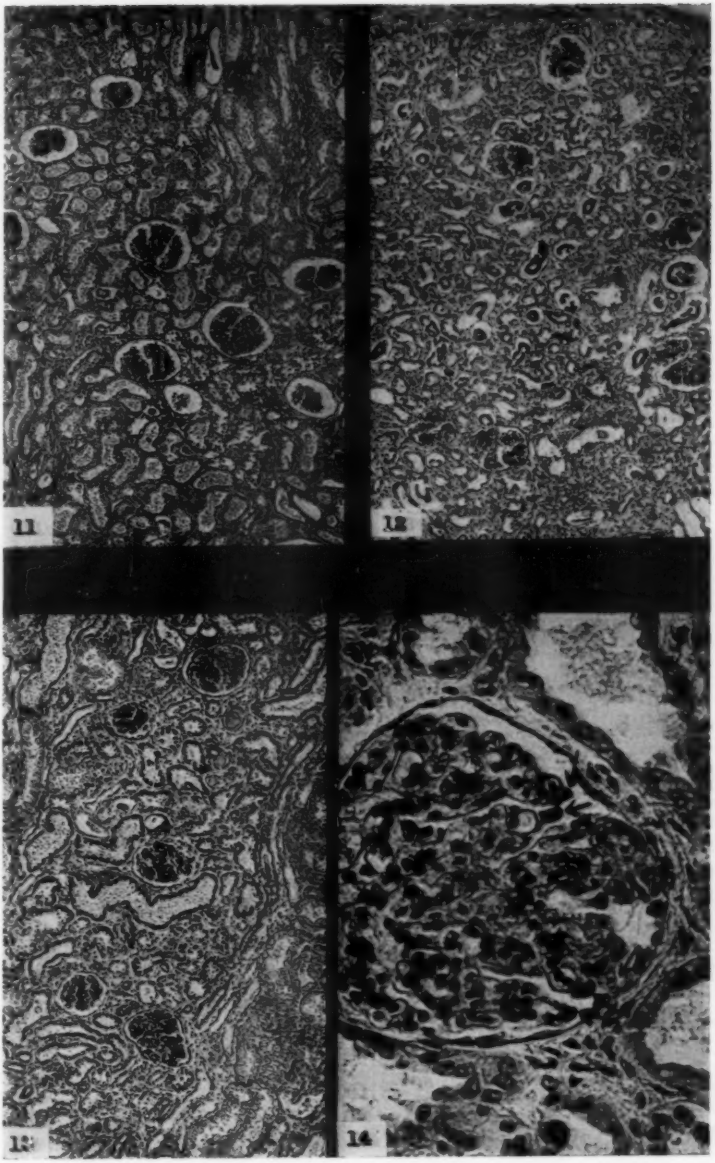
FIG. 17. Case 8, autopsy 7362. Nephrosis for 1 year. The photograph shows one of the focal scars described in the kidney of this case, like the scars seen in several others. They are sharply circumscribed, scattered at wide intervals, and contain groups of atrophied or scarred glomeruli with corresponding atrophied tubules.



FIGS. 1–3

FIGS. 4–6

FIGS. 7–10



FIGS. 11–14

FIGS. 15–17

ACID-BASE BALANCE OF GASTRIC JUICE, BLOOD AND URINE BEFORE AND AT INTERVALS AFTER STIMULATION OF THE GASTRIC JUICE BY HISTAMINE

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INTRODUCTION

To the clinician it is a matter of some moment to understand the effect of gastric secretion upon the acid-base changes of the blood and urine. The studies which heretofore have been reported in this connection have at most dealt with only one or two of the electrolytes involved; furthermore, they were generally limited to observations made upon either the blood or the urine. In the attempt to clarify the subject the following observations have been made and such interpretations and conclusions as seem indicated are described.

Dodds and Smith (1), in 1923, described the changes which occurred in the blood chlorides after meals. They found a drop, two to three milliequivalents per liter, for about forty-five minutes during gastric secretion and then a return to normal. Hubbard and Mumford (2), also Essen, Kauders and Porges (3), followed the urinary changes after meals. They found that in the great majority of cases in which free hydrochloric acid was secreted into the stomach, there was an alkaline post-prandial tide. Furthermore, in cases of achlorhydria, there was usually no alkaline tide. That there are other factors connected with this change in urinary reaction, has been demonstrated by Muschat (4) since he was able to influence the type of urinary change by altering the number and types of meals. Hubbard (5) believes that this irregularity is due to the changes in acid excretion during the course of twenty-four hours.

The change in blood chlorides following histamine injection has

been reported by Sarajichvili and Rafflin (6) for humans; they found that the chlorides were lowered. Similar observations were made on dogs by Hashimoto (7) with small doses, and by Drake and Tisdall (8) and Hiller (9) after large doses.

Bulger, Duff and Harrison (10), in an interesting and well conducted series of experiments on dogs during the excretion of gastric juice, were unable to find an increase of base. This was interpreted by them as representing chloride and water loss to the stomach in isotonic amounts and a retention of total base.

A considerable number of investigators have been interested in the CO_2 of the blood or alveolar air. Two main types of gastric stimulants have been used, food and histamine. After meals the CO_2 changes were usually determined upon the alveolar air. Higgins (11), Dodds (12), Bennett and Dodds (13), Brunton and Israels (14), Van Slyke, Stillman and Cullen (15), and Kauders and Porges (16), all reported a rise in alveolar CO_2 after ingestion of food. The last mentioned investigators say that such a change was found only in patients who were secreting an acid gastric juice.

Dodds and McIntosh (17) were unable to find an increase in the CO_2 of plasma in food-stimulated cases but do report an increase in the CO_2 of the red blood corpuscles. Hubbard (18), in 1928, tested the effect of a high carbohydrate meal on patients who were suffering from carbohydrate abnormalities and found an increase in titratable alkalinity of the blood after such meals. Van Slyke, Stillman and Cullen (15) found an increased plasma CO_2 capacity in most of their cases after the ingestion of food.

The results following the use of histamine as a gastric stimulant seem to fall into two classes, according to the size of the dose. Where a relatively large amount was given, there was always a fall in plasma CO_2; reports of work done on animals from Underhill and Ringer (19), Wallace and Pellini (20), Hashimoto (7), Boyd, Tweedy and Austin (21), and Hiller (9), all agree on this. Small doses have been given humans by Fonseca and de Carvalho (22), and by Delhougne (23), who found an increase of plasma CO_2 in subjects secreting hydrochloric acid in the gastric juice but not in those with achlorhydria; by Katzenelbogen (24), who found an increase in plasma CO_2 in four cases of acidosis; by Brunton and Israels (14), who reported a drop in alveolar CO_2.

Hashimoto (7) and Drake and Tisdall (8) found an increase of non-protein nitrogen in the plasma of dogs after large doses of histamine. From results of similar experiments Hiller (9) made the statement that "histamine injection affords an easily controlled means of producing an acute transient condition of tissue destruction in the body."

In their investigations upon cats, Derer and Steffanuti (25) found that histamine, given intravenously in large amounts, increased the concentration of the blood but decreased the serum proteins below the amounts found in normal blood. They thought that relative permeability of the vessels was the explanation.

METHODS

The studies herein reported were made on a group of 53 patients of the Johns Hopkins Gastro-intestinal Dispensary and the Medical Wards. Material for examination—gastric juice, alveolar air, blood, and urine—was obtained as follows: The patient reported to the clinic in the morning following a fifteen hour fast. The fasting specimen of gastric contents was completely removed by means of a duodenal tube and syringe and preserved under white oil. The method of collecting the gastric juice has been described in detail in a former report (40). At approximately the same time, samples of blood, urine and alveolar air were obtained to be used as controls (fasting). Histamine (ergamine acid phosphate), 0.005 mg. per pound of body weight, was injected hypodermically. Gastric juice was continuously collected by syphonage and syringe following this stimulation and separated into three one-half-hour lots. At the end of thirty, sixty and ninety minutes, samples of blood, urine and alveolar air were obtained.

The necessary determinations were made upon the gastric juice by the following methods. Hydrogen-ion concentration was determined by the colorimetric method, using Clark's (26) standards and indicators. Titratable acidity was measured by the conventional method, using dimethyl-amino-azo-benzene and phenolphthalein as indicators. Total chlorides were determined by the method of Van Slyke (27), bases according to the technic of Stadie and Ross (28), total acid-soluble phosphates by the method of Benedict and Theis (29), CO_2

content by the method of Van Slyke and Cullen (30), protein nitrogen, amino acids and ammonia by standard methods in which certain modifications were made (31–32).

Blood was obtained without stasis in the majority of cases and was always preserved under oil. A portion was oxalated and the remainder allowed to clot.

Alveolar air was obtained with the apparatus of Fridericia and analysed in accordance with his technic (33) for CO_2. The chlorides of the whole blood and serum were determined by the method of Whitehorn (34). Acid-soluble phosphates of the serum were determined as phosphate P by the method of Benedict and Theis (29). CO_2 content and capacity of the blood were measured by the method of Van Slyke and Stadie (30). The estimation of the total nitrogen of blood serum was carried out on 1 cc. by the Kjeldahl method (35) and the result determined by titration with freshly prepared 0.02N HCl. Non-protein nitrogen on the whole blood was estimated by the method of Folin and Wu (36). The total bases were determined on 1 cc. of serum by the method of Ross and Stadie (28).

Urine was collected in bottles containing white oil. The total volume of each specimen of urine was measured and the hydrogen-ion concentration determined by the method of Clark and Lubs (26). Because this is an open air method, there is reason to believe that the pH values in the more alkaline urines are somewhat high. The total acidity of the urine was determined by titration to a faint pink to phenolphthalein, which also gives a figure somewhat higher than the actual, but the error was approximately constant throughout. The total chlorides of the urine were estimated by the method of Volhard and Harvey (37). Inorganic orthophosphates of the urine were determined as phosphate P by the method of Fiske and Subbarow (38). CO_2 content of the urine was estimated on 1.00 cc. by the method of Van Slyke and Stadie (30). The total base of the urine was determined by the aeration method of Van Slyke and Cullen (39).

Complete data were obtained on 53 cases. To conserve space only representative cases are shown in tables A and B.

TABLE A

Complete data on patients secreting free hydrochloric acid into the gastric juice after histamine stimulation. Group I

CASE NO.	DIAGNOSIS	TIME	GASTRIC JUICE								BLOOD						URINE							
			pH	Volume	Free HCl	Total chlorides as chloride ion	Base	P as phosphate ion	Ammonia nitrogen	CO_2 as HCO_3 ion	Whole blood chlorides as chloride ion	Serum chlorides as chloride ion	P as phosphate ion	CO_2 of serum as HCO_3 ion	Protein as bound by base	Total base of serum	pH	Titratable acidity	Total base	Ammonia nitrogen	P as phosphate ion	Total chlorides as chloride ion	CO_2 content as HCO_3 ion	Volume
		minutes		*cc.*	*meq.**	*meq.*	*meq.*	*meq.*	*meq.*	*meq.*	*meq.*	*meq.*	*meq.*	*meq.*	*meq.*	*meq.*		*meq.*	*meq.*	*meq.*	*meq.*	*meq.*	*meq.*	*cc.*
100	Functional disorder	F	6.1	7	0				4.2		74	102	2.0	24.3	15.6	152	7.1	4	231	6	7	186	9.8	80
		30	3.2	18	2	86	76		4.2		70	101	1.8	27.8	16.9	156	7.1	4	225	8	7	181	9.2	100
		60	2.1	10	21	96	74		2.8		69	98	1.8	25.3	17.1	152	7.2	5	228	12		181	21.6	30
		90	6.1	8	0	96	92		4.2		76	98	1.6	24.0	16.2	154	7.2	6	264	12		224	22.4	40
101	Functional disorder	F	2.8	30	12	88	82	1.0	4.3		83	106	1.7		17.6	154	6.0	24	239	18	9	231	1.0	40
		30	1.9	50	36	110	84	0.6	2.4		79	104	1.8		17.5	158	6.0	24	224	16	10	229	1.0	30
		60	1.8	25	78	118	78	0.3	2.4		81	105	1.7	28.5	17.9	156	5.9	26	219	16	12	224	1.0	17
		90	1.7	40	50	131	84	0.3	2.7		80	105	1.6	27.4	18.2	158	5.9	42	124	40	15	173	1.0	11
104	Functional disorder	F	2.3	18	19	92	82	1.6	5.9		86		1.8	29.0		158	7.7	4	274	12	13	240	31.1	75
		30	1.5	22	76	131	60	0.8	4.0		77		1.7	29.5		152	7.9	7	140	4	6	142	30.1	95
		60	1.2	130	108	143	42	0.7	4.0		79		1.8	29.5		152	8.0	3	234	4	8	188	30.2	35
		90	1.9	25	50	110	70	1.0	4.0		80		1.8	29.0		156								
98	Duodenal ulcer	F	2.8	45	10	85	75	1.7	5.3		83	100	1.2	22.0	15.8	150	6.2	22	280	28	19	287		50
		30	1.6	70	70	121	50	0.8	4.0		76	95	1.2	22.0	17.1	150	6.0	44	280	40	26	325		20
		60	1.8	50	52	121	68	0.5	4.3		78	97	1.2	26.0	16.9	154	6.0	42	295	40	28	320		10
		90	1.9	30	28	108	82	1.1	3.9		80	103	1.2	22.0	16.9	154	6.0	44	295	40	28	329		10
99	Duodenal ulcer	F	2.1	25	42	108	50	0.5	4.0		79	99	2.0	24.8	17.2	150	6.6	24	259	40	29	276		90
		30	1.8	60	82	138	48	0.8	2.6		83	102	1.8	25.9	17.0	154	7.8	10	278	14	9	252	17.1	50
		60	1.6	60	94	141	48	0.6	2.9		83	102	1.7	25.2	17.3	155	8.0	3	276	4	4	238	23.1	30
		90	1.6	45	92	141	54	0.4	4.2		79	101	1.7	26.3	16.2	151	8.0	4	276	8	1	245	21.2	35

* Meq. = Milliequivalents per Liter.

TABLE B

Complete data on patients secreting no free hydrochloric acid into the gastric juice after histamine stimulation. Group II

CASE NO.	DIAGNOSIS	TIME	GASTRIC JUICE								BLOOD						URINE							
			pH	Volume	Free HCl	Total chlorides as chloride ion	Base	P as phosphate ion	Ammonia nitrogen	CO_2 as HCO_3 ion	Whole blood chlorides as chloride ion	Serum chlorides as chloride ion	P as phosphate ion	CO_2 of serum as HCO_3 ion	Protein as bound by base	Total base of serum	pH	Titratable acidity	Total base	Ammonia nitrogen	P as phosphate ion	Total chlorides as chloride ion	CO_2 content as HCO_3 ion	Volume
		minutes		*cc.*	*meq.**	*meq.*	*meq.*	*meq.*	*meq.*	*meq.*	*meq.*	*meq.*	*meq.*	*meq.*	*meq.*	*meq.*		*meq.*	*meq.*	*meq.*	*meq.*	*meq.*	*meq.*	*cc.*
112	Benign achlorhydria	F	8.0	60	0	70	112	3.1	6.5	30.0	83	110	1.8	21.0	16.3	150	6.5	21	222	40	23	248		130
		30	7.8	45	0	68	90	1.9	5.7	21.9	83	104	1.9	22.8	18.3	151	5.9	24	199	56	20	235		39
		60	7.6	30	0	108	112	2.7	6.8	17.0	81	105	2.1		18.3		6.0	24	166	65	17	228		27
		90	7.7	35	0	93	106	2.2	6.1	17.5	81	102	1.9	23.8	16.7	149	6.0	30	143	87	23	221		18
110	Pernicious anemia	F	6.7	15	0	108	113	1.9	6.5	5.7	92	105	3.1	27.2	15.1	154								
		30									87	105	2.9	26.8	15.8	157	7.1	13		77	29	217	9.1	
		60	7.1	15	0	137	140	1.4	6.2	4.7	87	102	2.9	26.4	15.8	152	5.7	20		54	12	134	1.0	
		90									85	106	2.5	26.8	15.9	151	5.7	18		54	12	117	1.0	
109	Gastric carcinoma	F	6.8	20	0	103	112	0.9	12.5		83	108	1.8		14.9	150	6.5	22	237	24	38	246	3.2	140
		30	5.8	20	9	113	114	0.8	12.5		80	102	1.8		16.2	153	7.0	11	261	22	26	267	5.0	30
		60	5.9	15	11	120	124	0.9	10.0		81	100	1.9		16.0	152	5.7	34	265	18	38	304		12
		90	6.8	30	0	112	130	1.4	9.8		77	102	1.9		15.5	155	5.7	38	268	20	32	300		8
111	Gastric carcinoma	F	8.0	12	0	102	118	3.5	7.2	8.3	72	97	1.3	25.0	15.4	164	6.6	13	117	33	19	107	3.2	
		30	7.7	6	0	97	93	3.0	7.0	6.5	73	99	1.7	25.4	15.2	168	6.4	13	132	20	19	114	3.2	
		60									72	100	1.5	25.7	15.3	166								
		90	7.8	18	0	100		3.1	6.2	4.8	74	97	1.3	25.4	15.4	168	6.0	20	129	25	22	121		

* Meq. = Milliequivalents per Liter.

EXPERIMENTAL

Group I. Gastric Secretion Containing Free HCl

Changes in gastric juice associated with secretion of free HCl. As detailed descriptions of the electrolyte (40), protein and non-protein nitrogen (31, 32, 41) measurements and changes in gastric juice are on record elsewhere, only an outline will be given here; one by which a comparison may be made with the electrolyte changes of blood and urine.

When stimulated by histamine, the individual with normal gastric response excreted an increased amount of free hydrochloric acid into the stomach. This was true whether the fasting juice contained free HCl or not.

The fasting specimens in which there was no free HCl contained free CO_2. Following the secretion of HCl the content of CO_2 fell within limits accounted for by bound CO_2.

In our present state of knowledge the important anions are: chloride, CO_2, phosphate and proteins. It is necessary to qualify this statement, for no complete studies have been made of the base bound by the proteins of gastric juice. In this report it is assumed that the bases are bound in the same manner as in the blood serum. It is realized that this may entail an error, but as so little protein was found, the error is of no great magnitude.

The cations consist of the total bases (sodium, calcium, magnesium, and potassium); the hydrogen-ion and ammonia. Amino acids and lactic acid have been found and quantification of the former has been carried out. However, not enough is known about them to determine their influence on the acid-base balance.

In the typical case, after histamine stimulation, there was an immediate increase in the volume of juice secreted. This was accompanied by an increase in the concentration of HCl in those cases in which it had been present in the fasting juice, and by its appearance, if it had not. There was a rise in the chloride averaging about 3 to 4 meq.[1] The concentration of phosphate declined from the initial figure of 1.0 to about 0.5 meq. As mentioned before, some free CO_2 disappeared, and there was a small drop in protein nitrogen.

[1] meq. = milliequivalents per liter.

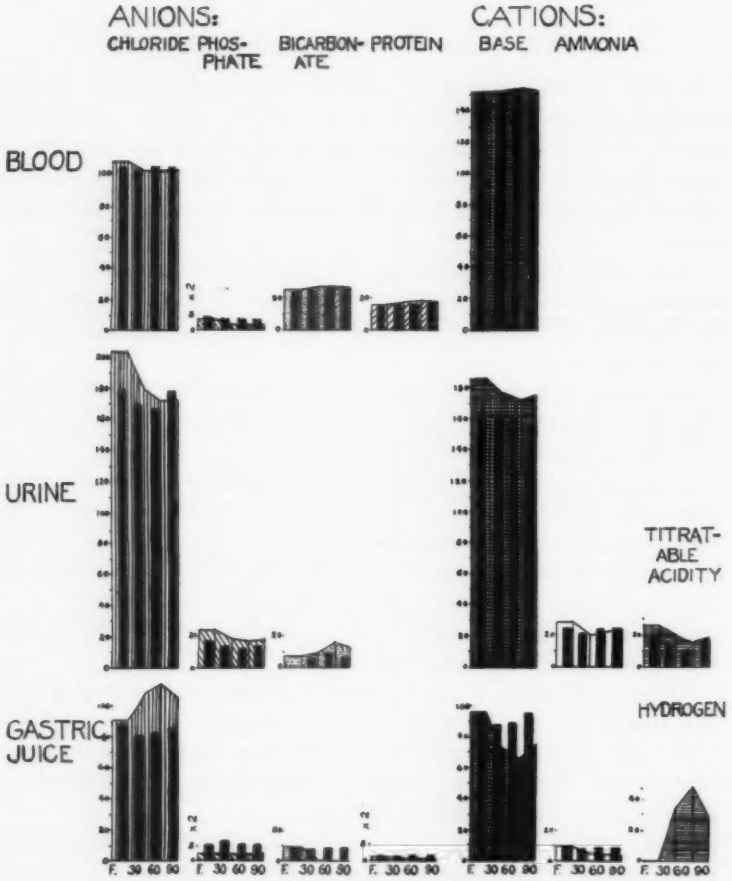

FIG. 1. TYPICAL PATTERN OF ACID-BASE CHANGES OCCURRING IN GASTRIC JUICE, BLOOD AND URINE, DURING THE PERIOD OF GASTRIC SECRETION PRODUCED BY HISTAMINE STIMULATION

The fine-point figures represent changes occurring when hydrochloric acid was secreted into the gastric juice. Average of 11 cases.

The black block figures represent changes occurring when no hydrochloric acid was secreted into the gastric juice. Average of 10 cases of achlorhydria.

As the effects of the stimulant wore off there was a tendency for the chloride to return to the prestimulation level. This change was coincident with a slight increase in phosphate and protein.

The cations underwent more marked changes. At the height of secretion, there was a notable decrease in the concentration of base which was approximately equal to the increase of free HCl, associated with a slight decrease of the concentration of ammonia. These changes are represented graphically in figure 1.

As the effects of the stimulant wore off there was a more marked decrease in the concentration of free hydrochloric acid than in that of the chloride. The falling off of free HCl was balanced by an increase of total base. From this type of reaction, it seems quite evident that the fall in titratable acidity is not due to regurgitation of alkaline duodenal contents, but is explained by the fact that the glands gradually secrete smaller and smaller amounts of HCl.

During the ninety-minute experimental period the average amount of chloride secreted into the stomach and, therefore, lost to the body was 152 meq.

Typical blood changes. In considering the blood and urine changes it must be remembered that gastric juice was being continuously removed by drainage and that there was a real loss to the body of these electrolytes.

The chloride of the blood was diminished during gastric secretion and striking changes were frequently seen. A *decrease* of 3 to 8 meq. of *serum* or *whole-blood chloride* was commonly seen. In some cases a fall of as much as 10 to 14 meq. was noted. The average diminution was about 7 meq.; this is equal to a change of approximately 7 per cent. Concomitantly with the decrease in chloride there was a real increase of CO_2 capacity and content. The average variation was about 6 to 7 per cent. Expressed as milliequivalents per liter the $BHCO_3$ increase was about 1.5 to 2.5 in normal cases. These changes and those of the other electrolytes may be followed in figure 1. Variations of phosphate paralleled those of the chloride. In 73 per cent of the cases there was a diminution of 0.05 to 0.20 meq. The average change was about 5 to 6 per cent.

It is particularly interesting to observe that, as the serum chloride diminished, the serum proteins increased. Expressed as base bound

by protein, the increase averaged about 1 meq. The total base of the serum varied in relation to the decrease in the concentration of chloride. When the latter fell between 4 and 8 meq., there was an associated elevation of base varying from 2 to 5 meq. When there was a marked fall in chloride, the base also tended to fall (between 3 and 6 meq.).

Typical urine changes. Accompanying the above changes there were equally interesting variations in the urine. In the first place, there was generally a greater amount of urine secreted in the first half hour than later. Furthermore, following the injection of histamine, in the great majority of instances, the urine became more alkaline as evidenced both by titration and by hydrogen-ion concentration. There was always agreement between the methods.

In those cases in which the urine tended to *become more alkaline*, fairly uniform electrolyte changes occurred. Of the anions, the chlorides and the phosphates usually decreased, and in a parallel manner. These changes were accompanied by an increase in CO_2 content. In general our results were similar to those of Marshall (42) and of Gamble (43). Of the cations, mention has already been made of the titratable acidity, which decreased. It is noteworthy that, although the concentration of the total base diminished, it usually decreased less than the chloride; that is, during gastric secretion base was excreted in relatively higher concentration than chloride so that the body lost base. This condition was perhaps necessitated by the increase of serum bicarbonate. The evidence for this point is strengthened by the finding of diminishing amounts of urinary ammonia. When the ammonia and phosphate excretions are compared, it is to be seen that they vary in almost similar proportions.

The average amount of chlorides excreted in the urine during the experimental period of ninety minutes was 233 meq. Added to the amount lost in the gastric juice, this gives an average total loss of 385 meq.

Atypical changes of Group I. There were found to be two more types of electrolyte variation, occurring with enough frequency and consistency to warrant some detailed mention. One exhibited itself in the blood and the other in the urine.

Blood. The typical change described above with decrease of blood

chloride was found in 82.8 per cent of the cases. The changes found in the remainder of the cases were associated with an *increase*, rather than a decrease, in *blood chloride*. The variation from the control was much less than in the typical case, averaging about 3 to 5 meq. Associated with this, there was an increase of CO_2 content and capacity (about equal to that seen in the main group). Variations in phosphates were also similar to those of the main group. When serum proteins were estimated, a decreased concentration was found associated with an increase of chloride. An unusual combination is presented: an increase of chloride and CO_2 content, and a decrease of protein. The arithmetical result of these changes is to increase the anion concentration in the serum, since the loss of protein does not compensate for the increase of Cl and CO_2. To balance this increase of anions, one might expect to find an increase of total serum base. There was an increase in total base averaging 3 to 5 meq., but this was of about the same order of magnitude as that which occurred in the typical group.

Urine. The variation of urine electrolytes described above as typical occurred in 77.6 per cent of the cases. In the remainder, certain atypical results were noted. In the first place the urine of these patients *became more acid* after histamine stimulation, and chloride, phosphate, base and ammonia were excreted in greater concentration.

These two atypical patterns did not appear to be related to one another. An analysis of results shows that the urine became more alkaline in about an equal number of instances in association with both types of blood acid-base change.

Group II. Gastric Secretion Containing No Free HCl

Gastric juice changes associated with achlorhydrias. The gastric juice of patients who did not secrete free HCl was quite different in many respects from that of those who secreted acid. Usually rather small volumes were collected during the experimental periods and the quantity varied little in the course of an experiment.

The diagnosis of patients with achlorhydria may be classified under four headings: Benign achlorhydria, pernicious anemia, gastric carcinoma and nephritis. All of the last group had high non-protein ni-

trogen in both blood and gastric juice. The ammonia nitrogen of the gastric secretion was also high. Two of these patients were in acidosis.

The range of chloride concentration in the gastric juice varied from 33 to 137 meq., but in the majority of instances was about 80. In four cases of nephritis consistently high levels of chloride were found. In the majority of individual cases there was but little variation in the different periods. However, in a number of cases the variation was considerable (from 20 to 40 meq.). The CO_2 concentration tended to vary in proportion to the chloride in any single case but the variation in individuals of the group was quite different; from 5 to 33 meq. were the changes noted. The concentration of phosphate was greater than in those subjects who secreted free HCl: between 2 and 8 meq., most frequently between 4 and 7 meq. In most instances it remained about the same throughout a single experiment. Protein remained about 0.75 meq. throughout the experimental period in the benign achlorhydrias and pernicious anemias. In gastric carcinoma and nephritis it was also constant, but much more elevated. The principal cations were ammonia and total base and, as no strong acid was excreted, their sum was about equal to that of the anions. As the total amount of ammonia was relatively small in the benign achlorhydrias (about 7 to 9 meq.) and varied but little, the rise or fall of the anions was almost entirely and quite directly matched by that of the total base in this group. As there was a definitely higher concentration of ammonia in the remaining achlorhydrias, it played a more important rôle in the acid-base balance of the gastric juice in those cases.

For comparison, the average amount of chloride secreted into the stomach and lost to the body during the ninety-minute period has been calculated. It amounts to 40 meq., only about one-fourth of the quantity secreted by the normal group.

Blood changes associated with achlorhydrias. The control estimations of the various blood electrolytes on the patients who secreted no free HCl into the gastric juice, revealed, in the larger number of cases, higher levels of chloride and phosphate than were found in the normal group. They also show lower values for total base and CO_2 content.

Following histamine stimulation the changes that ensued followed certain general patterns in the majority of the cases; but atypical forms were seen with considerably greater frequency than in the normal group. For the sake of clarity it may be permissible to outline roughly the two outstanding patterns of the electrolyte changes. Details are given below.

In 63.5 per cent of the cases there was a post-stimulation decrease in the chloride of whole blood and serum. The accompanying anion changes were an increased CO_2 (content and capacity) and protein, with a total irregularity in the behavior of the phosphate. There was a rise of total base which was greater than the measured increase of the anions. No explanation has been found for this phenomenon and one is loth to postulate an undemonstrated increase of organic acids. These changes are shown graphically in the black blocks of figure 1.

In 36.5 per cent of the cases there was an increase of the whole-blood and serum chloride. In a few cases there was an associated fall of the CO_2 content; however, in the greater proportion there was an increase. The serum protein fell as the chloride rose, while the phosphate again behaved in an unpredictable manner. The bases in every instance increased but no more than those of patients whose chlorides decreased. These changes were similar to those atypical blood changes in normal cases with the exception that the excursions of the individual electrolytes, excluding the phosphates, were smaller.

A detailed analysis of the achlorhydrias shows that in 63.5 per cent of the cases the changes of chloride concentration fell between the limits of 3 and 10 meq. In the majority of the cases the decrease was between 3 and 6 meq.

Bicarbonates in this second group rose in 83.2 per cent, the increase varying from 1 to 5 meq., usually between 1 and 3 meq.; consequently, it is evident that in the majority of cases with an increase of chloride, there was an associated rise of CO_2 content. It would be expected that, in these cases particularly, the greatest increase of base would be found, but analysis of the data does not reveal any greater rise of base than in the cases that showed the more common responses. This is probably due to the fact that in the cases under discussion the anion change was relatively slight.

The variation in the phosphate is characterized mainly by incon-

sistency. In 50 per cent of the cases there was a decrease which fell within the limits of 0.05 and 0.20 meq. In other patients a rise or no change was seen.

The level of the control bicarbonate ion concentration in Group II was lower than in Group I and, in association with this, the level of the total bases of the controls was lower in comparison with that in Group I. This was especially apparent in the nephritics. There were, however, a few patients in whom an abnormally high total base was demonstrated. A post-stimulation increase of base was seen in 79.2 per cent of the group (a finding closely in accord with the CO_2 content). The increase of base, with but rare exceptions, was between 1 and 5 meq. and varied somewhat with the change of chloride. Three types of change were found: an increase of chloride in connection with an increase of base; a slight decrease of chloride with the usual rise of base; and a more marked diminution in chloride with almost no change or a fall in base.

It is interesting that in 3 of the 4 cases in which the CO_2 content fell after histamine a coincident increase of both chloride and base occurred. The only instance in which there was a concomitant fall of both the bicarbonate and chloride, was in a patient with pernicious anemia, and this may have been connected with the fact that the patient secreted an amount of gastric juice unusual for an achlorhydria; there was a high chloride content in the gastric juice and a marked decline in the whole blood chloride (14 meq.).

Urinary changes associated with achlorhydria. The urinary changes cannot be described in the general way that was possible with Group I. As a whole, pH changes were of much smaller degree than in the acid-secreting group. In a number of instances the reaction remained almost constant; in 40 per cent there was either an increased acidity or a minimal variation after histamine. This is in marked contrast to the much more common excretion of an alkaline urine in the patients who secreted a normal gastric juice.

In the groups in which the *blood chloride decreased* there was a general tendency for the *urine to become more alkaline.* This was accompanied by a fall of urinary chloride and phosphate, and a decrease of CO_2 content. The cations showed a similar response, namely, a fall of total base and ammonia, and a decrease of titratable acidity.

These changes are typical only in that they occurred in the majority of cases. In an important number there was found one or more electrolyte changes quite at variance with those of the majority and it has not been possible to define these irregularities by any general pattern.

The urinary changes which take place as the *blood chloride decreases* are, perhaps, the most important findings in the patients with achlorhydria. In about an equal number of the cases the urine became more acid, more alkaline, or remained stationary. Those that varied showed far less change in pH and titratable acidity than any other group in the entire series. The variations of all the electrolytes were very small and in a number of instances the concentrations remained constant throughout the period of observation.

A group of cases in which the urinary change is worthy of note is that in which the reaction of the *urine became more acid* after histamine stimulation. The percentage of cases with this response is much larger in Group II than in Group I, especially if the patients in whom no change in reaction was found may be included. It comprises 40 per cent of the achlorhydrias as against 21 per cent of the former group. The changes were smaller in degree than those observed in the normals.

Individual cases. Many interesting phenomena were observed in the patients with nephritis. An outstanding result may be brought out by examining the data in each of the following cases. The first patient (Case 108) was a severe nephritic with blood N.P.N. of 225 mg. per cent. He died two days after these studies were made. The control specimen of gastric juice has a pH of 8.0 and contained a large amount of CO_2 (there was only the slightest bile tinge), and increased concentrations of phosphate and protein; the chloride and base were present in about normal amounts, but the ammonia N was tremendously elevated. Following histamine stimulation there was no increase in the volume of secretion, but the base, chloride and ammonia were all found in increased concentration. The phosphate decreased about 50 per cent and the protein remained approximately stationary. The loss of electrolytes from the body was so small that it seems impossible that it could be responsible for the marked changes that occurred in the blood. Consequently, these must, in large part, have been due to the histamine.

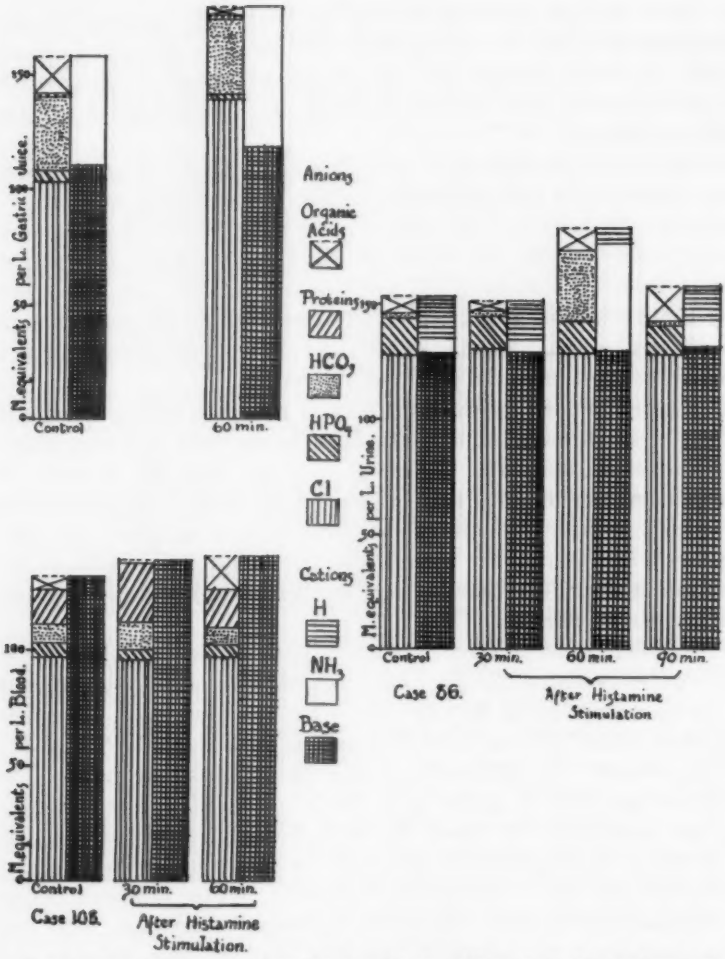

FIG. 2. Case 108, a severe nephritic in acidosis. Electrolyte changes in gastric juice and blood Especially noteworthy is the increased serum base and a corresponding increase in CO_2 content.

Case 86, also a severe nephritic. Electrolyte changes in urine. Especially noteworthy is the marked increase of ammonia nitrogen in a urine which became quite alkaline.

The chloride of the blood, which had been low in the control specimen, dropped from 97 to 95.8 meq. There was a simultaneous elevation of the CO_2 capacity and content from 8.4 to 12.0 meq. The serum protein also increased 1.4 meq. The base, which had been 132 meq., increased to 140. It is unfortunate that no urine could be collected from this patient. The changes described above are shown graphically in figure 2.

The second patient (Case 86) serves to illustrate an ammonia response which was seen with some frequency, *i.e.*, an increase of ammonia in an increasingly alkaline urine. This patient was also a nephritic, but less sick than the former. His blood N.P.N. was 160 mg. per cent and dropped to 124, 115 and 103 in the successive periods after histamine. His gastric juice in its various components was quite similar to that of the previous case, and the electrolytes of the blood showed similar but less marked initial derangement and response to histamine. The urine was acid and remained so at the thirty minute collection. At this time there was practically no change in any of the electrolytes. At the sixty minute collection the urine became quite alkaline. There was again practically no change in the excretion of chloride and base. There was, however, a marked increase in the CO_2 content (from practically 0 to 30 meq.). This was balanced by an increased output of ammonia (from 16 to 47 meq.).

In addition to the previous case there was one other (Case 111), in which the blood N.P.N. declined after histamine, in this instance falling from 89 to 73 mg. per 100 cc. to return again subsequently to the control level.

When this observation is considered in association with the remarkable increase of bicarbonate and of base, shown particularly by Case 108, there arises the entertaining idea that histamine may have some therapeutic rôle, even though a palliative one, in similar cases.

DISCUSSION

Cases secreting free HCl into the gastric juice

A study of the cases which secrete free HCl shows that, during the experimental period, a loss of chloride in the gastric juice was directly related to a decreased concentration of this ion in the blood and

urine. The fall of blood chloride was prompt and in the thirty minute period had usually reached its maximal limits. In the urine, however, the change was more gradual and the most marked decrease of chloride concentration was found at 60 minutes. The fall of blood chloride with the slight elevation of base was compensated by an increase of bicarbonate. In a small series of cases this was found to be accompanied by a rise of serum protein. This electrolyte disturbance gradually disappeared as the gastric secretion became smaller.

The changes reported can apparently be explained on the basis that the body lost fluid and chloride to gastric juice. Base was lost in much smaller amounts, as the secretion of neutral salt into the stomach was much less than that of the acid chloride. The excess base of the blood was immediately bound by CO_2 and the increase of protein and base must be in part due to dehydration.

By comparing the whole-blood and serum chlorides and assuming, as was presumably true, since the majority had normal red blood cell counts, that the hematocrit reading was normal, it may be seen that as the serum lost chloride so did the red cells. Consequently, there was an influx of tissue or intercellular fluids which were evidently mobilized relatively slowly. The reëstablishment of normal acid-base relations was due to the influx of these fluids and the cessation of the stimulus for gastric secretion.

The base of the urine, which became more alkaline, diminished in absolute concentration, as did the chloride, but was excreted in greater relative concentration, as though the body at that time did not need to preserve base. It would be interesting to know what would happen to the blood and urine base when gastric juice in large amounts was being lost over a long period of time. Although more chloride than base would be excreted, there would be a large amount of base lost to the body. It would seem reasonable to expect that in this type of case, in spite of an alkalosis, urinary ammonia excretion might be increased in order to save base. In 83.5 per cent of the cases reported ammonia diminished with a decrease of pH.

In only one patient (Case 45) was there a large enough secretion of gastric juice to remove sufficient chloride and base to approximate the situation outlined above. During the nine-minute observation period a total of 570 cc. of gastric juice was collected, containing 79 meq. of

chloride. During this period the whole blood chloride dropped from 89 to 72 meq. The phosphate of the serum fell from 2.32 to 1.78 meq. The bicarbonate varied but little at the periods observed. Owing to the extremely rapid loss of chloride into the stomach there may have been an early rise which soon terminated because base was also being lost (serum base dropped from 150 to 144 meq.).

The urine became quite alkaline and the chloride concentration decreased. The base concentration rose slightly at first, but in the last specimen, which was still quite alkaline, returned to the control level. The excretion of ammonia in this last specimen became quite elevated; evidently, since so much base was being lost through the gastric juice, the body was preserving base in this manner.

About 8 meq. of phosphate were lost to the body by gastric secretion during the ninety-minute period. This represents the phosphate contained in at least 200 cc. of serum and means a substantial loss. In response to this there was a diminution of its concentration in both blood and urine.

Achlorhydria

The loss of electrolyte through the gastric mucosa of the achlorhydrias averaged about 25 per cent of that in the other group. The changes in the acid-base balance of the blood and urine, in a way, reflected this difference in degree; for although in a number of instances there was a prompt drop in the blood chloride, the majority of cases showed less change than did those in the normal group.

It would seem that the ability or inability to secrete free HCl into the gastric juice was connected with something more than a simple gastric mucosal response. This idea is based on the fact that the percentage of chloride, acid soluble phosphate, CO_2 content, protein base, found in the blood of patients who were able to secrete free HCl into the gastric juice, differs distinctly from that of the second group. The dissimilarity affected all the substances. The differences were not seen in all of the cases but in a large enough percentage to have a real significance. In the achlorhydric group, the average of the whole blood chloride was found to be about 6 meq. higher. The phosphate in this second group was found to average about 4 mg. per 100 cc., instead of 3.5, as in the former group. Serum protein was

found to be slightly lower in the non-acid-secreting cases. One of the striking differences was seen in the CO_2 capacity and content, and the base; by both methods of estimation, it was shown that the serum base of the achlorhydrias was at a lower concentration than in the normal group. In making these comparisons those cases have been omitted in which base was obviously low and phosphate high, as in the nephritics. If these had been included the difference would have been greater.

The only outstanding difference noted between the initial urinary specimens of the two groups, was that the pH of the acid-secreting cases was generally less acid than that of the achlorhydrias. The average reaction in both groups was slightly acid.

Having established these differences in the initial specimens of the two groups, certain characteristics in the type, and in the degree, of post-stimulation response were found which further differentiated them. In both the blood and the urinary acid-base balances the average variations of the respective electrolytes were smaller in the achlorhydrias. This was true, no matter whether the response was of the typical or of the atypical type.

The difference between the groups is further emphasized by comparison of the types of response. It has been shown that post-stimulation increase of blood chloride was found in only 10 per cent of the acid-secreting group; in the second group such a change was noted in 22 per cent of the patients. The second difference is to be seen in the behavior of the bicarbonate. A slight fall of CO_2 capacity occurred in two of the patients who secreted free HCl. Of the patients who did not secrete free HCl, a decrease in CO_2 capacity was found in four. In three of these instances, there was a simultaneous fall of base. The other patient (Case 70) showed several unexplainable changes which may have been due to some technical error.

Whereas only 20 per cent of the urine specimens of the cases in Group I became more acid during the period of gastric secretion, 40 per cent of Group II either did not vary in pH or became more acid. In the cases in which the urine became more acid, the concentration of base and chloride in the last urinary specimen was greater than that in the corresponding specimen of the normal group.

To attribute the post-stimulation pattern of the achlorhydrias to

the loss of more chloride than base to the gastric juice, would be impossible, unless it could be shown that some other base, such as ammonia, was secreted in sufficient amounts to bring about this inequality; an inequality similar to that produced by the secretion of hydrochloric acid. The amount of ammonia in the gastric contents of the cases of benign achlorhydria was small and, as base and chloride were found to be excreted in almost equivalent amounts, it is most unlikely that the fall of blood chloride could be due to the secretion of ammonia in this group. Therefore, it would seem likely that through the influence of histamine chloride is transferred to the tissues.

From these observations it would seem, that in addition to whatever influence the injection of histamine may have on the body, the secretion of gastric juice containing hydrochloric acid has by itself a very direct action on the acid-base balance, as evidenced by the electrolyte changes in blood and urine. The difference in degree and, at times, in type of electrolyte response between those individuals who secreted free hydrochloric acid into the gastric juice and those who did not, points most strongly in this direction.

SUMMARY

A number of cases have been studied to observe the electrolyte changes in the gastric juice, blood and urine during the period of gastric secretion. Histamine was used as a stimulant and the gastric juice was continuously extracted during the period of observation. The cases have been described under two groups: I. those who were able to secrete free HCl into the gastric juice and II. those who were not.

The amount of salts lost from the body in Group I was about four times that lost in Group II.

1. In the blood of the first group the typical changes were a decrease of chloride and phosphate, and an increase of CO_2 content and serum protein. There was a slight rise of total serum base. This represents a state of relative alkalosis.

The urine became more alkaline in the majority of cases. Among the anions, chloride and phosphate fell while CO_2 increased. Of the cations, base, hydrogen-ion concentration and ammonia N fell.

Instances of atypical changes of both blood and urine have been described; also hypothetical explanations of these changes have been advanced.

2. In the achlorhydrias the variations in the majority of the cases were similar in kind but different in degree from those described above. The difference in degree consisted of a smaller loss of electrolyte in the gastric juice and correspondingly smaller variations in blood and serum.

In the initial specimen certain distinctive differences between the groups were noted.

In Group II the CO_2 capacity of the serum more frequently fell and the blood chloride more often rose, although the rises were small. In the urine the change of pH was apt to be less marked and in a larger percentage of cases the urine became more acid or remained unchanged.

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BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this journal.)

Diagnosis in Joint Disease. A Clinical and Pathological Study of Arthritis. By NATHANIEL ALLISON AND RALPH K. GHORMLEY. 196 pp. (*Wm. Wood & Co., New York, 1931.*)

This book is particularly confined to a consideration of etiological and pathological factors in reference to diagnosis. The authors stress particularly:

1. The etiological factors
2. Infected joint tissues
3. Changes which have taken place in these infected tissues.

Their careful study implies a coördination of the viewpoints of the Orthopedic Surgeon, the Clinician, the Roentgenologist, the Chemist and the Biologist. Their classification of arthritis is as follows:

1. Tuberculous Arthritis
2. Traumatic Arthritis
3. Arthritis associated with the formation of loose bodies
4. Pyogenic Arthritis
5. Arthritis of an uncertain origin, namely, the Proliferative and Degenerative Arthritis.

Biopsy has been frequently employed to clear up the diagnosis in cases heretofore resistant to treatment. The work is profusely illustrated with roentgenograms, and colored plates. The subject is presented in an elaborate form to which much time and thought must have been devoted.

E. D. W.

Surgery of the Stomach and Duodenum. By J. SHELTON HORSLEY. 260 pp. $7.50. (*C. V. Mosby Co., St. Louis, Mo., 1933.*)

The preface of this book states that it is largely written from the personal experiences of the author. Few men in America are so well qualified for such a task. The subject matter is handled in a masterly and entertaining manner, and holds the interest of the reader throughout. All unnecessary and extraneous details often found in textbooks are carefully avoided, yet each essential detail in the surgical procedures for the various diseases of the stomach and duodenum is clearly described. The book is well illustrated with many excellent drawings. The author does not hold the radical views of gastric surgery entertained by some surgeons, nor is he ultra-conservative. The rationale of the procedures he advocates is based on that thorough knowledge of the anatomy and physiology of the stomach so necessary to an understanding of the handling of pathological lesions. The reasons for each surgical step are clearly given. The book will delight those

interested in a clear exposition of the principles and practice of gastro-duodenal surgery.

A. R. K.

The Story of Childbirth. By Dr. Palmer Findley. Illust. 376 pp. (*Doubleday, Doran & Co., New York, 1933.*)

Designed for the lay student, this popular presentation is in no sense a guide for the pregnant woman, or prospective father. The material is nicely balanced with folk-lore, history and modern practice. The author discusses the taboos associated with menstruation, marriage, pregnancy and labor, and also the topic of maternal impressions. In setting forth modern scientific explanations of foetal amputations, he unfortunately omits Streeter's recent work. There is an interesting, profusely illustrated chapter on the birth customs of primitive peoples. The rôle of the midwife, past and present, is detailed. Here there is another unfortunate omission in the failure of the author to explore the curious "Hebammenbücher." The chapters on anaesthesia and puerperal infection are excellent—the best popular presentation the reviewer has yet encountered. The book contains a convincing but too conservative chapter on contraception, abortion and sterilization. Without mincing words the author sets before his readers the deplorable situation in this country with respect to maternal mortality. Altogether, Dr. Findley has published an extremely attractive and well-written book which does yeoman's service in dispelling much of the mysticism with which our medical predecessors enshrouded pregnancy and labor. The general plan of enlightening the laity as to the secrets of the obstetric art is commendable.

A. F. G.

Arteriosclerosis. A Survey of the Problem. Edited by Edmund V. Cowdry. [A Publication of the Joseph Macy Jr. Foundation.] Illust. Pp. 617. $5.00. (*The Macmillan Co., New York.*)

The objectives of the volume are three, *viz.*, to determine established data concerning arteriosclerosis; to ascertain and to formulate definitely the main problems awaiting solution; and to suggest the best means of attacking them. It can hardly be said that these admirable purposes have been fulfilled. The twenty-one chapters cover adequately the important aspects of the disease, and a great mass of pertinent information is assembled in a book of modest proportions. But, as each chapter has been undertaken by a different contributor, each has its peculiar merits and demerits. Most of the contributors have adopted a very broad attitude toward their respective subjects, but the presentation of the material in some chapters is coloured to a degree by personal opinion. There is not the uniform and rigid application of critical analysis to available data which might have made this publication the point of departure for future investigation. Problems bristle from every page but concrete suggestions for their solution are not so numerous. Whatever else may be gained, the reader will at least emerge with a full realization of the

magnitude and difficulty of the whole problem of arteriosclerosis. To the investigator, the excellent bibliographies which follow every chapter should prove most valuable.

G. L. D.

Neurology. By ROY G. GRINKER. 979 pp. $8.50. (*Charles C. Thomas, Springfield, Ill., 1934.*)

Of all the recent textbooks of neurology, this book approaches closest to the ideal. It is written in an easy style; it is interesting and up to date in its discussion of disease processes. The author has endeavored to bring recent advances in embryology, morphology and physiology to bear upon the problems of clinical neurology, and the result, in general, is good. But all this does enlarge the book to unwieldy proportions and for the sake of completeness introduces many data which are irrelevant. Particularly is this true of comparative neurology. A discussion of the corpus striatum of reptiles and birds has little known bearing on disease of the corpus striatum in man. Since we know so little of the functions of the corpus striatum, this perhaps serves as a foundation. The correlations which may be made at the boundary lines of different fields have small place in a book of clinical neurology for students, unless they actually illuminate the subject. For the specialist, on the other hand, all these facts add grist to the mill of his cerebral cortex.

The book is at its best when it reflects the opinions of the Chicago school of neurology and neuro-surgery. Thus, the chapter on brain tumors is excellent. The treatment of such rapidly expanding subjects as diseases of the autonomic nervous system is refreshing and adequate. This work is undoubtedly the best one available.

O. R. L.

The Renal Lesion in Bright's Disease. By THOMAS ADDIS and JEAN OLIVER. 629 pp. $16.00. (*Paul B. Hoeber, Inc., New York, 1931.*)

The object of this volume is to bring consideration of Bright's disease back to Bright's own notion of a study of the clinical complex and its cure "by a reference to morbid anatomy," which has been overlooked by too much concentration upon functional tests. The term "nephritis" is not adequate to describe a condition covering so many vascular and other lesions. The authors' classification based upon the renal lesion comprises—haemorrhagic, degenerative and arterio-sclerotic varieties. Three initial chapters cover the clinical aspects, three the pathological findings. The rest of the book is concerned with correlation of bedside, laboratory and microscopic data, with a terminal chapter on classification with reference to present and future viewpoints. The volume is handsomely printed and embellished with 170 full-page microscopic sections.

F. H. G.

Thomson & Miles' Manual of Surgery. By ALEXANDER MILES and D. P. D. WILKIE. Vols. 1, 2 & 3. $3.80 each. 8th edition. (*Oxford University Press, New York, 1931.*)

These three volumes constitute an excellent introduction to the subject of surgery. They are interestingly written and will appeal especially to the medical student.

W. C.